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CHARACTERIZATION OF DEMENTIA WITH LEWY BODIES (DLB) AND MILD COGNITIVE IMPAIRMENT USING THE LEWY BODY DEMENTIA MODULE (LBD-MOD)

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Abstract

INTRODUCTION: The NIA Alzheimer Disease Research Center program added the Lewy Body Dementia module (LBD-MOD) to the Uniform Data Set to facilitate LBD characterization and distinguish DLB from Alzheimer's disease (AD). We tested the performance of the LBD-MOD.

METHODS: The LBD-MOD was completed in a single-site study in 342 participants: 53 controls, 78 AD, and 110 DLB, 79 mild cognitive impairment due to AD (MCI-AD) and 22 MCI-DLB.

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AUTHOR CONTRIBUTIONS

Dr. Galvin was involved in the conceptualization, data curation, formal analysis, funding acquisition, methodology, supervision, and writing of original draft, revisions, and editing. He approves of the final version and ensures the accuracy and integrity of the work.
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CONFLICTS OF INTEREST

JEG is the creator of the Lewy Body Composite Risk Score scale used in this study as a cross validation for the LBD-MOD. The other authors report no conflicts of interest

RESULTS: DLB differed from AD in extrapyramidal symptoms, hallucinations, apathy, autonomic features, REM sleep behaviors, daytime sleepiness, cognitive fluctuations, timed attention tasks and visual perception. MCI-DLB differed from MCI-AD in extrapyramidal features, mood, autonomic features, fluctuations, timed attention tasks, and visual perception. Descriptive data on LBD-MOD measures are provided for reference.

DISCUSSION: The LBD-MOD provided excellent characterization of core and supportive features to differentiate DLB from AD and healthy controls while also characterizing features of MCI-DLB.

Keywords

Dementia with Lewy Bodies; DLB Module; Dementia; Mild Cognitive Impairment; Alzheimer's Disease; Alzheimer Disease Center Program; Uniform Data Set; Lewy Body Composite Risk Score

INTRODUCTION

Dementia with Lewy bodies (DLB) [1] is the second most common cause of neurodegenerative dementia after Alzheimer's disease (AD) [2] affecting approximately 1.4 Million Americans [3,4] and belongs under the umbrella of Lewy body dementia (LBD) along with Parkinson's disease dementia. Prevalence estimates of DLB range from 0% to 5% in the general population and from 0% to 30.5% of all dementia cases [5,6]. In a systematic review of 22 studies, DLB incidence rates range between 0.5 to 1.6 per 1000 person-years, accounting for 3–7% of dementia cases [6,7], while DLB prevalence estimates range from 0.02 to 63.5 per 1000, increasing with advancing age.

The clinical picture of DLB revolves around the identification of visuospatial, executive, and attentional deficits, rather than marked episodic memory impairment that characterizes AD [8–10]. These cognitive symptoms together with parkinsonism, cognitive fluctuations, visual hallucinations, and rapid eye movement sleep behavioral disorder (RBD) are core features of DLB [1]. Cognitive fluctuations, while quite specific for DLB, are the most difficult to elicit [11,12]. Visuospatial deficits are common in DLB and represent a very early and sensitive marker, especially when Lewy body and AD pathologies are mixed [8–10]. Participants with DLB generally perform better on episodic memory tests than AD participants for any given level of dementia severity and are more likely to improve with cued recall and recognition [8–10]. Participants with DLB generally show milder naming deficits than participants with AD on measures of confrontation naming, while DLB participants may perform worse than AD in category and letter fluency tasks [4], due in part to difficulties with verbal initiation in timed tasks and attentional deficits. Hallucinations and delusions are common in DLB, elicited primarily through informant interviews and less so from participant reports or direct observation by clinicians [13]. Visual hallucinations in DLB tend to occur early in the course of the disease, frequently appearing as detailed, well-formed dysmorphic or little people, or animals [4,13]. Depression, anxiety, and apathy are common in both DLB and AD [14], however mood disturbance may be early presenting symptoms of Lewy body disorders [15,16]. Autonomic dysfunction is a common feature in DLB [17] and may precede cognitive or motor symptoms by more than a decade [6]. Symptomatic orthostasis

is probably the most impactful manifestation of autonomic nervous system dysfunction, but other features include thermoregulatory dysregulation, sialorrhea, urinary dysfunction, constipation or obstipation, erectile dysfunction, impotence, and changes in libido [18]. Other constitutional features include anosmia and excessive daytime sleepiness [4,6,18].

Another evolving concept is that of mild cognitive impairment (MCI) due to DLB (MCI-DLB) [19,20]. Criteria for MCI due to AD (MCI-AD) have been published [21] providing a standardized approach to diagnosing MCI-AD in the clinical setting and a crucial framework for research, biomarker discovery and clinical trials. More recently, operationalized criteria for MCI-DLB have been described providing a context to study MCI-DLB and the unique cognitive-onset, delirium-onset, and psychiatric-onset presentations of DLB [19].

However, at the present time, DLB remains a challenge to diagnose, particularly outside of expert centers. This leads to long delays in diagnosis leading to significant burden to participants, families, and caregivers [22–24] and hinders research advances. While the DLB consensus criteria have excellent specificity [1], until recently there has been no standardized way to assess signs and symptoms. Two recent developments were the creation and publication of the Lewy Body Composite Risk Score (LBCRS) [25,26] and the Assessment Toolkit for Lewy Body Dementia (also known as DIAMOND Lewy) [27]. The LBCRS was validated in 256 participants compared with the Clinical Dementia Rating (CDR) [28] and gold standard measures of cognition, motor symptoms, function, and behavior. The LBCRS was able to differentiate: (a) DLB from AD; (b) DLB from other dementias, and (c) MCI-DLB from MCI-AD [25]. The DIAMOND Lewy toolkit provides detailed worksheets for completion by the clinician that correspond to the consensus criteria for DLB and Parkinson's disease dementia [27].

The Alzheimer Disease Center (ADC) program funded by the National Institute of Aging (NIA) has pioneered many groundbreaking advances in AD research, in part by providing a Uniform Data Set (UDS) of clinical, cognitive, functional and behavioral symptoms in a standardized fashion across the funded centers [29,30]. The UDS is also available for non-ADC researchers to utilize so that research projects funded under different mechanisms can be harmonized with data from the National Alzheimer Coordinating Center [31]. A specialized module for Frontotemporal Lobar Degeneration (FTLD) was developed [32–34] to improve classification and advance research of FTLD and its subtypes. In 2015, NIA convened a workgroup of dementia and movement disorder experts to develop a module for DLB and Parkinson's disease dementia (LBD-MOD). The LBD-MOD was designed to evaluate the clinical, cognitive, and behavioral symptoms associated with DLB and Parkinson's disease dementia, standardize data collection on LBD across centers for data entry into the National Alzheimer Coordinating Center database, and harmonize with research efforts by dementia and movement disorder researchers. It was subsequently revised in 2020 to further streamline data collection, make several scales optional, and reduce participant, caregiver, and researcher burden. The LBD-MOD is an optional component to the UDS meant to be applied when relevant to specific clinical groups or to address specific research or clinical questions. We present the first study of the utility of the LBD-MOD to (a) characterize DLB, (b) discriminate DLB from cognitively normal controls and AD, and (c) discriminate MCI-DLB from MCI-AD.

METHODS

Study Participants

This descriptive, cross-sectional, single-site study was conducted in 342 participant-informant dyads who fell into one of 5 diagnostic groups: healthy controls, DLB, AD, MCI-AD, or MCI-DLB attending our center for clinical care or participation in cognitive aging research. As the goal of this project was to evaluate the ability of the LBD-MOD to discriminate DLB from AD or MCI-DLB from MCI-AD, other diagnoses were excluded from these analyses. During the visit, the participant and informant underwent a comprehensive evaluation including the CDR and its sum of boxes (CDR-SB) [28], other components of the UDS version 3.0 (UDSv3.0) [29,30] and the LBD-MOD. The participants underwent a clinical interview to generate a CDR, the scales from the UDSv3.0 were completed, a complete neurological examination was performed, the UDSv3.0 psychometric battery was completed, and the LBD-MOD components were completed. These instruments were then used to determine the presence or absence of cognitive impairment, if present stage the cognitive impairment, and then assigned a diagnosis based on the information gathered during the assessment informed by published diagnostic criteria. All components of the assessment are part of standard of care at our center [35] and protocols in the clinic and research projects are identical. A waiver of consent was obtained for the clinic, while prospective research participants provided written informed consent. This study was approved by the University of Miami Institutional Review Board.

Clinical Assessment

Standardized scales from the UDSv3.0 were administered to the informants to provide ratings of cognition, function, and behavior [29,30]. Activities of daily living were captured with the Functional Activities Questionnaire (FAQ) [36]. Dementia-related behaviors and psychological features were measured with the Neuropsychiatric Inventory (NPI) [37]. The risk of vascular contributions to dementia was assessed with the modified Hachinski scale [38]. When available, clinical neuroimaging studies were reviewed for vascular or other pathology by a Board-certified neurologist. The CDR [28] was used to determine the presence or absence of dementia and to stage its severity; a global CDR 0 indicates no dementia; CDR 0.5 represents MCI or very mild dementia; CDR 1, 2, or 3 correspond to mild, moderate, or severe dementia. The CDR-SB was calculated by adding up the individual CDR categories (range: 0–18; higher scores supporting more severe impairment). Diagnoses were determined in a consensus conference using standard criteria for MCI [21], AD [2], DLB [1], vascular contributions to cognitive impairment and dementia (VCID) [39], and FTLD [40]. Individuals with VCID, FTLD, and other forms of dementia were not considered further for this study. As our center does not see primary movement disorder cases, Parkinson’s disease dementia was not included in this study.

The LBD-MOD was developed as an optional module to complement the full UDS for investigators interested in DLB and Parkinson’s disease dementia that could be compared to healthy controls and AD to develop and refine LBD phenotypic characterization. Since the LBD-MOD components were chosen to specifically detect LBD clinical features as described in published clinical criteria for Lewy body disorders, there would be little reason

to complete the LBD-MOD on individuals with other forms of neurodegenerative disease unless the investigator had a specific reason to do so. This strategy is similar to other optional UDS modules such as the Frontotemporal lobar degeneration module or the Down's syndrome module.

Cognitive Assessment

Each participant was administered the UDSv3.0 neuropsychological test battery [30] at the time of the visit to assess their cognitive status. The psychometrist was unaware of the diagnosis or CDR. The Montreal Cognitive Assessment [41] was used for a global screen. The rest of the battery included the 15-item Multilingual Naming Test (MINT); Animal naming; Numbers Forward and Numbers Backward; and Trailmaking A and B. The UDSv3.0 contains a paragraph recall test of episodic memory, however for this study we substituted a list learning test, the Hopkins Verbal Learning Task [42] that provided immediate recall, delayed recall and recognition scores that may help differentiate DLB from AD [8,9].

The LBD Module Components

In addition to the UDSv3.0, the LBD module (Table 1) was administered during the same single setting. The LBD-MOD contains additional measurements that assess autonomic and constitutional features, extrapyramidal signs, sleep, parasomnias, alertness, and cognitive fluctuations (See https://www.alz.washington.edu for LBD-MOD forms and documentation). The LBD-MOD collects information from both participants and informants and was collected in a single session by a transdisciplinary team of a neurologist, nurse practitioners, social workers, and research coordinators. Items for the inclusion into the LBD-MOD by the workgroup were selected to (a) harmonize with other national and international efforts in AD and Parkinson's disease, and (b) be freely available without licensing fees. The LBD-MOD takes on average 20 minutes to complete the participant section and 20 minutes to complete the informant sections (these may be done in parallel). The completion of the UDSv3.0 takes 90–120 minutes to complete. Individuals with more impaired cognition may take longer. Autonomic and constitutional features were captured by a checklist of 23 features derived in part from the Non-Motor Symptoms Scale [43] and Scales for Outcomes in Parkinson's disease-Autonomic Dysfunction (SCOPA-AUT) [44] used in studies of Parkinson's disease. The checklist rates the presence and absence of sialorrhea, dysphagia, libido and sexual performance, unplanned weight loss, changes in taste and smell, hyperhidrosis, cold and heat intolerance, double vision, gastroparesis, constipation, obstipation, incomplete emptying of the bladder, urinary frequency and strength of urination, bowel and bladder incontinence, orthostatic hypotension and syncope. A total score (range 0–23) was calculated by adding the number of features endorsed. Ratings of nighttime sleep disturbances (range 0–5), sleep quality (range 1–7), and daytime sleepiness (range 0–6) were captured by the SCOPA-Sleep [45]. Parasomnias were captured by the Mayo Sleep Questionnaire [46] rating the presence or absence of RBD, periodic leg movements of sleep, restless legs syndrome, and obstructive sleep apnea. Daytime alertness was rated on a 1–10 Likert scale ("Rate the participant's general level of alertness for the past 3 weeks on a scale from 0 to 10") anchored by "Fully and normally awake" (scored 10) and "Sleep all day" (scored 0) [46]. Cognitive fluctuations were captured by

the Mayo Fluctuation Questionnaire [11] which contains 4 yes/no questions (range 0–4) capturing excessive daytime sleepiness, lethargy, incoherent or illogical thinking, and staring with scores greater than 2 supporting the presence of fluctuations. Extrapyramidal features were captured by the original version of the Unified Parkinson's Disease Rating Scale (UPDRS) [47] and the modified Hoehn and Yahr scale. Finally, a novel test of visual perception, a modified version of the Noise-Pareidolia test [48] was administered. The modified Noise-Pareidolia test contains 20 images of ink blots of which 8 contain human faces. The participant is asked to determine whether a face is present or not, and if present identify its location. Four scores are obtained: Correct Faces (range 0–8), Correct Noise (range 0–12), Total Correct (range 0–20), Pareidolias (range 0–20). Scores of greater than 2 Pareidolias are reported to be sensitive to detection of DLB [48]. We then re-analyzed the 342 individuals creating scores on the LBCRS [25] to provide an independent, validated rating scale to differentiate DLB from cognitively normal controls and AD, and MCI-DLB from MCI-AD.

Statistical Analyses

Analyses were conducted with IBM SPSS Statistics v26 (Armonk, NY). Descriptive statistics were used to examine demographic characteristics, informant rating scales, dementia staging, and neuropsychological testing. As this is a cross-sectional study, only baseline visits were considered. Most participants received their first diagnosis at the end of the visit and were not previously on medications. Therefore, medications were not considered in the analyses. Analyses were first conducted comparing cognitively normal controls with AD and DLB cases. Upon analyses, we determined that the DLB group were more impaired than the AD group. Therefore, for continuous variables, a two-way analysis of variance (ANOVA) with interaction effect was initially used to estimate differences according to group membership (cognitively normal controls, AD, and DLB) and CDR. None of the interaction terms were significant with $p<.05$, so two-way ANOVA without interaction (additive model) was used because the relationship between group membership and continuous variable did not depend on severity. Overall p-values between group means were reported with post-hoc comparisons using Tukey's honestly significant difference (HSD) to test for differences between DLB and AD. Chi-square tests were used for categorical data across the three groups and for comparisons between DLB and AD. We then examined for differences between MCI-AD with MCI-DLB using one-way ANOVA for continuous variables and Chi-square test for categorical variables. Multiple comparisons were addressed using the Bonferroni correction.

RESULTS

Sample Characteristics

The mean age of the participants was 75.5±9.2 years (range 38–98) with a mean education of 15.7±2.7 years (range 8–20). The sample was 54.8% male, 95.9% White, with 5.0% reporting Hispanic ethnicity. ApoE ε4 carriers comprised 35.7% of the sample. The participants had a mean CDR-SB of 4.8±4.7 (range 0–18), a mean modified Hachinski score of 0.7±0.9 (range 0–5), a mean FAQ score of 9.5±9.8 (range 0–30), a mean NPI score of 6.7±6.1 (range 0–28), a mean UPDRS score of 10.8±13.9 (range 0–88), and a mean

MoCA score of 18.7±7.1 (range 1–30). The mean age of the informants was 56.2±14.9 years (range 20–76) with a mean education of 16.0±2.5 years (range 4–20), and 66.9% were women. Informants consisted of spouses (65.2%), adult children (21.0%), or other individuals (13.8%) with 69.1% reporting living with the participant and having daily contact. The sample covered a range of cognitively normal controls (CDR 0=53), MCI or very mild dementia (CDR 0.5=130), mild dementia (CDR 1=77), moderate dementia (CDR 2=61) and severe dementia (CDR 3=21). Consensus clinical diagnoses included 53 cognitively normal controls, 78 AD, and 110 DLB. There were 101 MCI cases divided between MCI-AD (n=79) and MCI-DLB (n=22).

Comparison Between Healthy Controls, AD and DLB Cases

The sample characteristics for the cognitively normal controls, AD and DLB cases with post-hoc comparisons between AD and DLB are presented in Table 2. As expected, there were more men in the DLB group compared with the cognitively normal controls and AD cases (p<.001) [1,4,6]. DLB cases were more impaired than AD cases by the CDR (1.6±0.8 vs. 1.3±0.7; p=.001) with more CDR 3 cases (16.4% vs. 3.8%, χ^2=11.5, p=.009). Cognitively normal controls were significantly different than AD and DLB cases in all demographic characteristics (except for education) and dementia rating scales (all p-values<.001). The DLB cases had more functional impairment as measured by the FAQ (p<.001), more behavioral impairments as measured by the NPI (p=.002), and more motor impairment as measured by the UPDRS (p<.001).

We then explored group differences between individual items contained within the CDR, FAQ and NPI that are part of the standard UDSv3.0. There was no difference between DLB and AD for the Memory or Orientation CDR domain, however significant differences were seen for the other four CDR domains (all p-values <.001). Individual item analyses for the FAQ (Table 3) demonstrate that shopping alone (FAQ question 3; p=.001) and playing games (FAQ question 4; p=.002) were significantly worse for DLB compared with AD. Individual item analyses for the NPI (Table 4) demonstrated a higher presence of hallucinations in DLB (35.2% vs. 4.8%, p<.001) and greater severity scores (0.6±0.9 vs. 0.1±0.5, p<.001). There was also a trend towards more nighttime behavioral disturbances in DLB (64.8% vs. 38.1%, p=.006) and greater severity scores (1.3±1.2 vs. 0.6±0.8, p<.001). Worse severity scores were also reported for apathy (p<.001) in DLB.

Autonomic and Constitutional Features Captured in the DLB Module

The presence of many individual autonomic and constitutional features and well as the total number of features discriminated cognitively normal controls from AD and DLB (Table 5). DLB participants experienced significantly more sialorrhea (p<.001), dysphagia (p=.001), problems with sexual performance (p<.001), and orthostatic hypotension (p=.001) compared with AD and had a higher total burden of autonomic and constitutional features (6.7±3.6 vs. 3.6±2.4; p<.001). Additional marginal differences were seen for double vision (p=.005), sense of smell (p=.04), cold intolerance (p=.01), incomplete emptying of the bladder (p=.01), urinary frequency (p=.02), and obstipation (p=.01).

Sleepiness, Parasomnias, Fluctuations, and Alertness Captured in the DLB Module

Table 6 displays the results from the SCOPA-Sleep scale, Mayo Sleep Questionnaire, and Mayo Fluctuation Questionnaire. DLB participants experienced more daytime sleepiness (p<.001), more RBD symptoms (p<.001), were more likely to snort or choke during sleep (p=.001) and have lower levels of daytime alertness (p<.001) than AD. There were significant differences in the presence of all 4 components as well as total scores in the Mayo Fluctuation Questionnaire in DLB compared with AD. Additional marginal differences were seen in periodic leg movements of sleep (p=.03) and restless leg syndrome (p=.01).

UDS Neuropsychological Tests in the DLB Module

Comparison of the UDSv3.0 neuropsychological test battery is shown in Table 7. Of the elements contained in the test battery, Trailmaking A completion times were slower in DLB (p<.001), while the MINT scores were lower in AD (p<.001). An additional episodic memory measure, the Hopkins Verbal Learning Test was administered to incorporate list learning and a recognition test. DLB performed better than AD on the delayed recall (p<.001) and recognition (p<.001) portions of the task. An addition to the LBD-MOD was the Noise Pareidolia test. There was no difference between DLB and AD for the correct faces score but DLB performed significantly worse on the correct noise, total correct, and total pareidolia scores (all p-values<.001).

Comparison of MCI-AD and MCI-DLB

We repeated the analyses for each component of the LBD-MOD comparing MCI-AD vs. MCI-DLB (Table 8). Features differentiating MCI-DLB from MCI-AD captured in the DLB module included depression (p=.004), anxiety (p=.005), UPDRS scores (p<.001), total autonomic features (p<.001) with constipation (p<.001), and obstipation (p=.004), total fluctuation scores (p<.001), performance on Trailmaking A (p=.003) and Trailmaking B (p=.001) tests, and total correct (p=.001) and total pareidolia (p=.005) scores on the Noise-Pareidolia test.

Alignment of Classification of the DLB Module to the Lewy Body Composite Risk Score

Finally, we completed the LBCRS on each participant to provide a cross-validation of the LBD-MOD items. Table 9 compares the LBCRS scores first for cognitively normal controls, AD and DLB cases, and then between MCI-AD and MCI-DLB. DLB is significantly different (all p-values<.001) from AD across all 10 items and total LBCRS score which are also captured as part of the LBD-MOD: bradykinesia, rigidity, postural instability, and rest tremor in UPDRS, daytime sleepiness in SCOPA-Sleep, illogical thoughts and staring spells in Mayo Fluctuations Questionnaire, hallucinations in NPI, RBD in Mayo Sleep Questionnaire, and orthostatic hypotension and other signs of autonomic insufficiency in the Autonomic Features Checklist. Comparing the MCI groups, significant differences were seen in bradykinesia (p<.001), rest tremor (p=.004), and total LBCRS scores (p<.001).

DISCUSSION

The LBD-MOD was created to assist researchers in the characterization of Lewy body diseases and foster cross-center collaborative DLB and Parkinson's disease dementia research. Differentiation of DLB, and to a lesser extent PDD, from AD is a diagnostic challenge, even at expert centers. Further, although consensus diagnostic criteria exist, determination of how best to capture core and supportive features and how to study them in a systematic fashion has been difficult. The LBD-MOD was designed to address these challenges and we demonstrate here that it was successful. The LBD-MOD adds specialized scales and tests that tap into the core, supportive, and suggestive features of DLB without duplicating features already captured as part of the UDSv3.0. Although designed as a research instrument, the LBD-MOD could be used in clinical practice. If used in clinical practice, the LBD-MOD should be used in addition to other standard components of the cognitive evaluation (e.g., history, neurologic examination, laboratory testing, imaging).

We found that the LBD-MOD provided excellent characterization of these key clinical features to clinically differentiate DLB from AD and cognitively normal controls while also providing a research format to build the evidence base to characterize MCI-DLB. Components of the standard UDS captured for all participants enrolled in the NIA ADC program that offered some differentiation between DLB and AD included components of the CDR, FAQ and NPI, however the UDSv3.0 could not fully capture the core, supportive or suggestive features of DLB [1]. The LBD-MOD added new instruments capturing features not previously part of the UDSv3.0 including an autonomic features checklist, standardized validated scales on extrapyramidal signs, sleep, parasomnias and cognitive fluctuations, and a new neuropsychological measure – the Noise Pareidolia test [48]. Each of these new components provided useful information to discriminate DLB from AD and help characterize MCI-DLB as distinct from MCI-AD. At the present it is not clear that any one component of the LBD-MOD is superior to another as each component examines non-overlapping clinical or cognitive features. Future revisions of the UDSv3.0 and its optional modules may address this. Factors contained in the LBD-MOD that discriminate DLB from AD, and MCI-DLB from MCI-AD match variables that discriminate between these disorders using an independent validation instrument, the LBCRS [25]. Both the LBCRS and the DIAMOND LEWY tools are essentially checklist to summarize the presence of LBD features, however the checklist require the clinicians or researchers to know what questions to ask and what signs to look for. The LBD-MOD provides standardized, validated tools to capture and quantify individual LBD features and provide a platform to compare LBD to cognitive normal controls or other neurodegenerative diseases.

There is no one sign or symptom that definitively distinguishes DLB from AD, and the two disorders share many common features and pathology [1,4]. The signs and symptoms of AD and DLB may resemble each other in the early stages, and many participants may "evolve" with what seems to be a clear early presentation of AD, later changing to DLB. There are cases of AD that develop Parkinsonism, particularly late in the clinical course, however if no other core features (e.g., hallucinations, fluctuations, RBD) were present, this case would be classified clinically as AD. This study only considered clinical diagnoses, but it should be

noted that many cases of AD have Lewy bodies at autopsy, while the majority of DLB cases have AD pathology [1,4,6].

However, with careful evaluation, DLB can be distinguished from AD by application of consensus criteria and use of indicative biomarkers [1]. The LBD-MOD provides an inventory of features that when collectively examined provide a full clinical characterization of DLB as a distinct clinical entity from AD and permits the study of prodromal presentations that are hypothesized to make up MCI-DLB [19]. This clinical distinction is performed in the absence of biomarkers and does not preclude the fact that individuals might have co-existing pathologies.

There are several limitations in this study. The LBD-MOD was created by dementia and movement disorder experts from the United States. Future revisions could consider research findings and features described by investigators in other parts of the world [49,50]. The LBD-MOD was validated in the context of an academic research setting where the prevalence of MCI and dementia in general, and DLB in particular are high, and the participants tend to be highly educated and predominantly White. Validation of the LBD-MOD in other clinical and research settings, other countries, and with a more diverse sample is needed. The LBD-MOD also needs to be tested in individuals with differing levels of education and in other languages. It was also validated in a single center by a transdisciplinary clinical research team all trained by the first author. Multi-site studies are needed to better understand inter-rater reliability. The LBD-MOD is currently being used by the NIA-funded ADRCs and the NINDS-funded Parkinson's disease biomarker program grants so multi-site papers may be available in the future. As this is a cross-sectional study, the longitudinal properties of the LBD-MOD still need to be elucidated. Biomarkers were not collected as part of this study, therefore comparisons of the LBD-MOD to imaging and fluid biomarkers of AD, DLB and other neurodegenerative diseases is needed. In this study, only cognitively normal controls, DLB and AD were studied. The performance of the LBD-MOD in other dementia etiologies such as Parkinson's disease dementia, VCID and FTLD are needed.

Findings from this study will be helpful in providing the initial evidence base for the use of the LBD-MOD in clinical research. The LBD-MOD appears to provide sufficient clinical discrimination between DLB and AD so that it can aid in diverse clinical research programs such as case-ascertainment in epidemiological studies, biomarker studies, cross-sectional and longitudinal studies, and clinicopathological correlation. Further, we were able to demonstrate the LBD-MOD to discriminate between MCI-AD and the more recent construct of MCI-DLB. The LBD-MOD ease of use may also facilitate its use in busy clinical settings where time is limited, and physicians are currently challenged with limited tools to diagnose DLB and its prodromal stages [25,27]. Improved detection and diagnosis of DLB with validated instruments such as the LBD-MOD can help to advance research and therapeutic developments to better serve the DLB community.

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REFERENCES

1. McKeith IG, Boeve BF, Dickson DW, et al. Diagnosis and management of dementia with Lewy bodies: fourth consensus report of the DLB consortium. Neurology 2017;89:88-100 [PubMed: 28592453]
2. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging–Alzheimer's association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011;7:263–269. [PubMed: 21514250]
3. Lewy Body Dementia Association. www.lbda.org. Accessed 9/29/20
4. Galvin JE. Lewy Body Dementia: Clinical Diagnosis and Management. Prac Neurology 2019;18:67–71
5. Zaccai J, McCracken C, Brayne C. A systematic review of prevalence and incidence studies of dementia with Lewy bodies. Age Ageing, 2005;34:561–566 [PubMed: 16267179]
6. Galvin JE, Bras JT. Neurobiology of Lewy Body Dementias: Animal and Human Studies. In: Neurobiology of Mental Illness. Charney DS, Nestler EL (Eds). Oxford University Press, New York, NY; 2018. pp 737–750.
7. Hogan DB, Fiest KM, Roberts JI, et al. The prevalence and incidence of dementia with Lewy bodies: a systematic review. Can J Neurol Sci 2016;43 Suppl 1:S83–95 [PubMed: 27307129]
8. Karantzoulis S, Galvin JE. Update on dementia with Lewy bodies. Curr Transl Geriatr Exp Gerontol Rep 2013;2:196–204. [PubMed: 25379359]
9. Karantzoulis S, Galvin JE. Discriminating Alzheimer disease from other major forms of dementia. Expert Rev Neurotherap, 2011;11:1579–1591
10. Donaghy PC, Barnett N, Olsen K, Taylor JP, McKeith IG, O"Brien JT. Symptoms associated with Lewy body disease in mild cognitive impairment. Int J Geratr Psych 32:1163–1171, 2017
11. Ferman TJ, Smith GE, Boeve BF, et al. DLB fluctuations: specific features that reliably differentiate DLB from AD and normal aging. Neurology 2004;62:181–187. [PubMed: 14745051]
12. Escandon A, Al-Hammadi N, Galvin JE. Impact of cognitive fluctuations on neuropsychological performance in aging and dementia. Neurology 2010;74:210–217. [PubMed: 20083796]
13. Dudley R, Aynsworth C, Mosimann U, et al. A comparison of visual hallucinations across disorders. Psychiatry Res. 2019;272:86–92. [PubMed: 30579187]
14. Moylett S, Price A, Cardinal RN, et al. Clinical Presentation, Diagnostic Features, and Mortality in Dementia with Lewy Bodies. J Alzheimers Dis. 2019;67:995–1005. [PubMed: 30776008]
15. Thaipisuttikul P, Lobach I, Zweig Y, Gurnani A, Galvin JE. Capgras Syndrome in Dementia with Lewy Bodies. Int Psychogeriatr 2013;25:843–849. [PubMed: 23211760]
16. Galvin JE, Malcom H, Johnson DK, Morris JC. Personality traits distinguishing dementia with Lewy bodies from Alzheimer disease. Neurology 2007;68:1895–19017. [PubMed: 17536045]
17. Sezgin M, Bilgic B, Tinaz S, Emre M. Parkinson's Disease Dementia and Lewy Body Disease. Semin Neurol. 2019;39:274–282. [PubMed: 30925619]
18. Palermo G, Del Prete E, Bonuccelli U, Ceravolo R. Early autonomic and cognitive dysfunction in PD, DLB and MSA: blurring the boundaries between α-synucleinopathies. J Neurol. 2020;6 27:1–13. On-line ahead of print
19. McKeith IG, Ferman TJ, Thomas AJ, et al. Research Criteria for the Diagnosis of Prodromal Dementia with Lewy Bodies. Neurology 2020;94:743–755. [PubMed: 32241955]
20. Hamilton CA, Matthews FE, Donaghy PC, et al. Cognitive Decline in Mild Cognitive Impairment With Lewy Bodies or Alzheimer Disease: A Prospective Cohort Study. Am J Geriatr Psychiatry. 2020;8 8:S1064–7481(20)30437–1. On-line ahead of print
21. Albert MS, DeKosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging–Alzheimer's

association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011;7:270–279. [PubMed: 21514249]

22. Galvin JE, Duda JE, Kaufer DI, Lippa CF, Taylor A, Zarit SH. Lewy body dementia: The caregiver experience of clinical care. Parkinson Rel Disord, 2010;16:388–392
23. Galvin JE, Duda JE, Kaufer DI, Lippa CF, Taylor A, Zarit SH. Lewy body dementia: Caregiver burden and unmet needs. Alz Dis Assoc Disord, 2010;24:177–181
24. Zweig Y, Galvin JE. Dementia with Lewy Bodies: The Impact of Disease on Participants and Caregivers. Alz Res Therapy 2014;6:21–28
25. Galvin JE. Improving the clinical detection of Lewy Body Dementia with the Lewy Body Composite Risk Score. Alzheimers Dement 2015;1:316–324.
26. Ryu HJ, Kim M, Moon Y, et al. Validation of the Korean Version of the Lewy Body Composite Risk Score (K-LBCRS). J Alzheimers Dis. 2017;55:1395–1401. [PubMed: 27834773]
27. Thomas AJ, Taylor JP, McKeith I, et al. Development of assessment toolkits for improving the diagnosis of the Lewy body dementias: feasibility study within the DIAMOND Lewy study. Int J Geriatr Psychiatry. 2017;32:1280–1304 [PubMed: 27928840]
28. Morris JC. The Clinical Dementia Rating (CDR): Current version and scoring rules. Neurol, 1993;43:2412–2414
29. Beekly DL, Ramos EM, Lee WW, et al. ; NIA Alzheimer's Disease Centers. The National Alzheimer's Coordinating Center (NACC) database: The Uniform Data Set. Alzheimer Dis Assoc Disord. 2007;21:249–258 [PubMed: 17804958]
30. Weintraub S, Besser L, Dodge HH, et al. Version 3 of the Alzheimer Disease Centers' Neuropsychological Test Battery in the Uniform Data Set (UDS). Alzheimer Dis Assoc Disord. 2018;32:10–17. [PubMed: 29240561]
31. [9/29/20] The National Alzheimer Coordinating Center. https://www.alz.washington.edu/WEB/forms_lbd.html Accessed
32. Ritter AR, Leger GC, Miller JB, Banks SJ. Neuropsychological testing in pathologically verified Alzheimer disease and frontotemporal dementia: how well do the uniform data set measures differentiate between diseases? Alzheimer Dis Assoc Disord 2017;31:187–191. [PubMed: 28005562]
33. Miyagawa T, Brushaber D, Syrjanen J, et al. Use of the CDR plus NACC FTLD in mild FTLD: Data from the ARTFL/LEFFTDS consortium. Alzheimers Dement 2020;16:79–90 [PubMed: 31477517]
34. Gefen T, Teylan MA, Besser L, Pollner E, Moshkovich A, Weintraub S. Measurement and characterization of distinctive clinical phenotypes using the Frontotemporal Lobar Degeneration Module (FTLD-MOD). Alzheimers Dement 2020;16:918–925. [PubMed: 32400973]
35. Galvin JE, Valois L, Zweig Y. Collaborative transdisciplinary team approach for dementia care. Neurodegener Dis Manag. 2014;4:455–469 [PubMed: 25531688]
36. Tappen RM, Rosselli M, Engstrom G. Evaluation of the Functional Activities Questionnaire (FAQ) in cognitive screening across four American ethnic groups. Clin Neuropsychol. 2010;24:646–661. [PubMed: 20473827]
37. Kaufer DI, Cummings JL, Ketchel P, et al. Validation of the NPI-Q, a brief clinical form of the Neuropsychiatric Inventory. J Neuropsychiatry Clin Neurosci. 2000;12:233–239. [PubMed: 11001602]
38. Rosen WG, Terry RD, Fuld PA, Katzman R, Peck A. Pathological verification of ischemic score in differentiation of dementias. Ann Neurol. 1980;7:486–488. [PubMed: 7396427]
39. Skrobot OA, O'Brien J, Black S, et al. The Vascular Impairment of Cognition Classification Consensus Study. Alzheimers Dement. 2017;13:624–633 [PubMed: 27960092]
40. Olney NT, Spina S, Miller BL. Frontotemporal Dementia. Neurol Clin. 2017;35:339–374. [PubMed: 28410663]
41. Nasreddine ZS, Phillips NA, Bédirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc. 2005;53:695–699. [PubMed: 15817019]

42. Shapiro AM, Benedict RH, Schretlen D, Brandt J. Construct and concurrent validity of the Hopkins Verbal Learning Test-revised. Clin Neuropsychol. 1999;13:348–358. [PubMed: 10726605]

43. van Wamelen DJ, Martinez-Martin P, Weintraub D, Schrag A, Antonini A, Falup-Pecurariu C, Odin P, Ray Chaudhuri K; International Parkinson, Movement Disorder Society Parkinson Disease Non Motor Study Group. The Non-Motor Symptoms Scale in Parkinson's disease: validation and use. Acta Neurol Scand. 2020 8 19. doi: 10.1111/ane.13336. Online ahead of print.

44. Visser M, Marinus J, Stiggelbout AM, Van Hilten JJ. Assessment of autonomic dysfunction in Parkinson's disease: the SCOPA-AUT. Mov Disord 2004;19:1306–1312 [PubMed: 15390007]

45. Marinus J, Visser M, van Hilten JJ, Lammers GJ, Stiggelbout AM. Assessment of sleep and sleepiness in Parkinson disease. Sleep 2003;26:1049–1054. [PubMed: 14746389]

46. Boeve BF, Molano JR, Ferman TJ, et al. Validation of the Mayo Sleep Questionnaire to screen for REM sleep behavior disorder in a community-based sample. J Clin Sleep Med. 2013;9:475–480. [PubMed: 23674939]

47. Fahn S, Elton RL, UPDRS program members. Unified Parkinson's Disease Rating Scale. In Fahn S, Marsden CD, Goldstein M, Calne DB (Eds). Recent Developments in Parkinson's Disease, vol 2. MacMillan Healthcare Information, Florham Park, NJ.: 1987 p153–163, 293–304.

48. Yokoi K, Nishio Y, Uchiyama M, Shimomura T, Iizuka O, Mori E. Hallucinators find meaning in noises: pareidolic illusions in dementia with Lewy bodies. Neuropsychologia. 2014;56:245–254. [PubMed: 24491313]

49. Oliveira FF, Machado FC, Sampaio G, et al. Neuropsychiatric feature profiles of patients with Lewy body dementia. Clin Neurol Neurosurg 2020;194:105832 [PubMed: 32311617]

50. Oliveira FF, Machado F, Sampaio G, et al. Contrasts between patients with Lewy body dementia syndromes and ApoE e3/e3 patients with late-onset Alzheimer disease dementia. Neurologist 2015;20:35–41. [PubMed: 26280289]

RESEARCH IN CONTEXT

Systematic Review:

The authors reviewed the published literature on the characterization of dementia with Lewy bodies (DLB) and mild cognitive impairment due to DLB (MCI-DLB). There are no current publications describing the use of the Lewy Body Dementia module (LBD-MOD) of the National Alzheimer's Coordinating Center.

Interpretation:

Our findings support that the LBD-MOD provided excellent characterization of core, supportive, and suggestive features to differentiate DLB from Alzheimer's disease (AD) and cognitively normal controls while also providing important characterizing features of MCI-DLB as distinct from MCI due to AD.

Future Directions:

The LBD-MOD was created to assist researchers in the characterization of Lewy body diseases and foster cross-center collaborative DLB and Parkinson's disease dementia research. Future studies will focus on longitudinal characterization, the utility of the LBD-MOD in other forms of dementia, and validation against fluid and imaging biomarkers and clinicopathologic relationships.

Table 1:

Components of Revised LBD-MOD

Component	Constructs Measured	# Items	Score Range	Source of Information	Time to Complete (min)
Autonomic Features Checklist	Autonomic and Constitutional Symptoms	23	0–23	Informant	3–5
Mayo Fluctuation Questionnaire	Cognitive Fluctuations	4	0–4	Informant	1–2
Mayo Sleep Questionnaire	Parasomnias	8	n/a[1]	Informant	2–3
Expanded NPI questions	Delusions, Hallucinations, Anxiety and Apathy	4	n/a[1]	Informant	3–5
SCOPA-Sleep	Nighttime Complaints, Daytime Sleepiness, and Sleep Quality	12	1–40	Informant	3–5
UPDRS – Part III	Extrapyramidal features	27	0–108	Participant	7–10
Noise Pareidolia	Visual illusions and Misidentifications	20	0–20	Participant	10

KEY: NPI=Neuropsychiatric Inventory; SCOPA=Scales for Outcomes in Parkinson's Disease; UPDRS=Unified Parkinson's Disease Rating Scale

[1]Scale determines presence or absence of symptoms, no score is generated

Table 2:

Sample Characteristics

Variable	Controls (n=53)	AD (n=78)	DLB (n=110)	Overall p-value	Post-hoc AD vs DLB
Age, y	67.6 (10.0)	79.7 (8.0)	77.7 (7.6)	<.001	.23
Sex, %M	30.8	44.9	72.7	<.001	**<.001**
Education, y	16.1 (2.2)	15.2 (2.8)	15.4 (2.8)	.17	.91
Hachinski	0.5 (0.6)	0.7 (0.8)	0.9 (1.1)	.02	.15
FAQ	0.1 (0.5)	13.6 (8.5)	17.0 (8.9)	<.001	**<.001**
NPI	1.4 (1.9)	7.6 (5.5)	10.2 (6.5)	<.001	**.002**
UPDRS	2.7 (3.5)	5.4 (6.4)	23.8 (16.4)	<.001	**<.001**
Hoehn & Yahr	0.2 (0.5)	0.3 (0.8)	2.5 (1.1)	<.001	**<.001**
CDR	0.0 (0.0)	1.3 (0.7)	1.6 (0.8)	<.001	**<.001**
CDR-SB	0.1 (0.2)	6.6 (3.6)	8.7 (4.8)	<.001	**<.001**
Memory	0.0 (0.0)	1.3 (0.7)	1.4 (0.7)	<.001	.19
Orientation	0.0 (0.1)	1.2 (0.8)	1.3 (0.8)	<.001	.02
Judgment/Problem Solving	0.1 (0.2)	1.4 (0.7)	1.8 (0.8)	<.001	**<.001**
Community Affairs	0.0 (0.0)	1.1 (0.7)	1.5 (0.8)	<.001	**<.001**
Home/Hobbies	0.0 (0.0)	1.1 (0.8)	1.6 (0.9)	<.001	**<.001**
Personal Care	0.0 (0.0)	0.5 (0.7)	1.2 (1.0)	<.001	**<.001**

Mean (SD) or %

KEY: AD=Alzheimer's disease; DLB=Dementia with Lewy bodies; FAQ=Functional Activities Questionnaire; NPI=Neuropsychiatric Inventory; UPDRS=Unified Parkinson's Disease Rating Scale; CDR=Clinical Dementia Rating; CDR-SB=CDR Sum of boxes

Bold indicates post-hoc significance for AD vs DLB after correction for multiple comparisons (corrected p-value<.003)

Table 3:

Comparison of FAQ Constructs between Cognitively Normal Controls, Alzheimer Disease, and Dementia with Lewy Bodies

FAQ Question	Controls (n=53)	AD (n=78)	DLB (n=110)	Overall p-value	Post-hoc AD vs DLB
Writing check, paying bills	0.0 (0.0)	1.6 (1.2)	2.1 (1.2)	<.001	.03
Assembling tax records	0.0 (0.0)	1.5 (1.3)	1.9 (1.2)	<.001	.06
Shopping alone	0.0 (0.0)	1.3 (1.2)	1.9 (1.1)	<.001	**.001**
Playing games	0.0 (0.0)	0.8 (0.9)	1.3 (1.2)	<.001	**.002**
Heating water	0.0 (0.0)	0.8 (1.0)	1.1 (1.2)	<.001	.09
Preparing balanced meal	0.0 (0.0)	0.9 (1.2)	1.4 (1.3)	<.001	.02
Current events	0.0 (0.1)	1.1 (0.9)	1.3 (1.2)	<.001	.36
Paying attention	0.0 (0.1)	0.8 (0.9)	1.1 (1.0)	<.001	.09
Remembering appointments	0.0 (0.2)	1.6 (0.9)	2.0 (1.0)	<.001	.01
Traveling outside neighborhood	0.0 (0.0)	1.8 (1.3)	2.0 (1.1)	<.001	.31

Mean (SD)

KEY: AD=Alzheimer’s disease; DLB=Dementia with Lewy bodies; FAQ=Functional Activities Questionnaire

Bold indicates post-hoc significance for AD vs DLB after correction for multiple comparisons (corrected p-value<.005)

Table 4:

Comparison of NPI Constructs between Cognitively Normal Controls, Alzheimer Disease, and Dementia with Lewy Bodies

Variable	Symptoms Present (%)					Severity Scores (Mean±SD)				
	Controls (n=53)	AD (n=78)	DLB (n=110)	Overall p-value	Post-hoc AD vs DLB	Controls (n=53)	AD (n=78)	DLB (n=110)	Overall p-value	Post-hoc AD vs DLB
Delusions	2.3	16.7	28.2	.002	.17	0.0 (0.1)	0.2 (0.5)	0.5 (0.9)	.001	.09
Hallucinations	0.0	4.8	35.2	<.001	**<.001**	0.0 (0.0)	0.1 (0.5)	0.6 (0.9)	<.001	**<.001**
Agitation	18.2	42.9	56.3	<.001	.17	0.2 (0.4)	0.6 (0.7)	0.9 (0.9)	<.001	.05
Depression	22.7	53.7	69.0	<.001	.10	0.3 (0.6)	0.8 (0.9)	1.1 (0.9)	<.001	.21
Anxiety	9.1	45.2	42.3	<.001	.76	0.1 (0.4)	0.6 (0.8)	0.6 (0.9)	<.001	.98
Elation	9.1	0.0	4.2	.13	.18	0.1 (0.3)	0.0 (0.0)	0.1 (0.3)	.238	.48
Apathy	4.5	47.6	71.8	<.001	.01	0.0 (0.2)	0.7 (0.9)	1.3 (1.1)	<.001	**.001**
Disinhibition	9.1	23.8	19.7	.17	.61	0.1 (0.2)	0.3 (0.7)	0.4 (0.8)	.063	.97
Irritability	27.3	41.5	60.5	.002	.05	0.3 (0.4)	0.5 (0.7)	1.0 (1.0)	<.001	.02
Aberrant Motor	0.0	23.8	33.8	<.001	.26	0.0 (0.0)	0.4 (0.8)	0.7 (1.1)	<.001	.19
Nighttime Behaviors	20.5	38.1	64.8	<.001	.006	0.2 (0.5)	0.6 (0.8)	1.3 (1.2)	<.001	**<.001**
Appetite	9.3	42.9	45.7	<.001	.77	0.1 (0.3)	0.6 (0.8)	0.8 (1.0)	<.001	.50

Mean (SD) or %

KEY: AD=Alzheimer's disease; DLB=Dementia with Lewy bodies; NPI=Neuropsychiatric Inventory

Bold indicates post-hoc significance for AD vs DLB after correction for multiple comparisons (corrected p-value<.005)

Table 5:

Comparison of LBD-MOD Autonomic Feature Checklist Constructs between Cognitively Normal Controls, Alzheimer Disease, and Dementia with Lewy Bodies

Variable	Controls (n=53)	AD (n=78)	DLB (n=110)	Overall p-value	Post-hoc AD vs DLB
Dribbles saliva, %	0.0	0.0	18.4	<.001	**<.001**
Difficulty swallowing, %	2.0	1.4	17.3	<.001	**.001**
Increased interest in sex, %	5.9	5.5	14.3	.09	.63
Decreased interest in sex, %	15.7	26.0	33.7	.06	.28
Problems with sexual performance, %	31.4	19.2	55.1	<.001	**<.001**
Weight loss (not due to dieting), %	0.0	26.0	30.6	<.001	.51
Change in sense of taste, %	7.8	15.1	26.5	.01	.07
Change in sense of smell, %	5.9	11.0	23.5	.008	.04
Excessive sweating, %	5.9	8.2	7.1	.88	.79
Cold intolerance, %	21.6	38.4	58.2	<.001	.01
Heat intolerance, %	9.8	13.7	21.4	.15	.19
Double vision, %	3.9	1.4	13.3	.007	.005
Difficulty digesting food, %	3.9	9.6	15.3	.09	.27
Constipation, %	5.9	28.8	40.8	<.001	.10
Obstipation, %	7.8	17.8	35.7	<.001	.01
Bowel incontinence, %	9.8	11.0	22.4	.05	.05
Incomplete bladder emptying, %	11.8	17.8	34.7	.003	.01
Weak urine stream, %	5.9	8.2	21.4	.008	.02
Urinary Frequency, %	13.7	28.8	46.9	<.001	.02
Urinary Incontinence, %	9.8	28.8	44.9	<.001	.03
Lightheaded/Dizzy when standing, %	9.8	23.3	49.0	<.001	**.001**
Lightheaded when prolonged standing, %	7.8	9.6	32.7	<.001	**<.001**
Fainting, %	2.0	6.8	5.1	.46	.63
Total Features, Mean (SD)	1.9 (2.7)	3.6 (2.4)	6.7 (3.6)	<.001	**<.001**

Mean (SD) or %

KEY: AD=Alzheimer's disease; DLB=Dementia with Lewy bodies

Bold indicates post-hoc significance for AD vs DLB after correction for multiple comparisons (corrected p-value<.002)

Table 6:

Comparison of LBD-MOD Sleep, Parasomnia, Fluctuation, and Alertness Constructs between Cognitively Normal Controls, Alzheimer Disease, and Dementia with Lewy Bodies

Variable	Controls (n=53)	AD (n=78)	DLB (n=110)	Overall p-value	Post-hoc AD vs DLB
SCOPA-Sleep, Nighttime, Mean (SD)	3.6 (3.1)	3.8 (3.1)	3.9 (4.0)	.90	.99
SCOPA-Sleep, Sleep Quality, Mean (SD)	2.6 (1.4)	2.8 (1.5)	3.1 (1.8)	.236	.41
SCOPA-Sleep, Daytime Sleepiness, Mean (SD)	2.1 (2.0)	3.4 (3.4)	6.4 (4.6)	<.001	**<.001**
Mayo Sleep: RBD, %	17.3	20.5	64.5	<.001	**<.001**
Mayo Sleep: PLMS, %	2.0	15.4	29.1	<.001	.03
Mayo Sleep: RLS, %	9.6	9.1	22.7	.02	.01
Mayo Sleep: Snort, %	16.0	15.4	37.3	.001	**.001**
Mayo Sleep: Apnea, %	14.9	19.4	27.3	.21	.26
Alertness, Mean (SD)	9.3 (1.1)	8.1 (1.6)	6.4 (2.1)	<.001	**<.001**
Mayo Fluctuations Total, Mean (SD)	0.3 (0.6)	1.2 (0.9)	2.7 (1.3)	<.001	**<.001**
Drowsy, %	16.3	30.3	70.7	<.001	**<.001**
Sleeps >2hrs, %	2.0	11.8	55.2	<.001	**<.001**
Flow of ideas, %	2.0	36.4	75.9	<.001	**<.001**
Stares, %	4.1	20.0	51.7	<.001	**.002**

Mean (SD) or %

KEY: AD=Alzheimer's disease; DLB=Dementia with Lewy bodies; SCOPA= Scales for Outcomes in Parkinson's disease

RBD=Rapid eye movement sleep behavioral disorder; PLMS=Periodic leg movements of sleep; RLS=Restless legs syndrome

Bold indicates post-hoc significance for AD vs DLB after correction for multiple comparisons (corrected p-value<.004)

Table 7:

Comparison of UDS and LBD-MOD Neuropsychological Test Battery between Cognitively Normal Controls, Alzheimer Disease, and Dementia with Lewy Bodies

Test Variable	Controls (n=53)	AD (n=78)	DLB (n=110)	Overall p-value	Post-hoc AD vs DLB
MoCA	26.6 (2.5)	13.8 (6.0)	14.2 (5.9)	<.001	.75
Numbers Forward	7.4 (1.4)	6.0 91.50	6.4 (1.5)	<.001	.21
Numbers Backward	5.6 (1.50	3.6 (1.60	3.6 (1.4)	<.001	.93
Trailmaking A, seconds	29.5 (10.9)	73.3 (42.1)	98.3 (50.2)	<.001	**<.001**
Trailmaking B, seconds	70.2 (41.1)	153.3 (41.1)	164.9 (33.8)	<.001	.22
Animal Naming	20.7 (4.5)	9.1 (4.8)	9.7 (4.7)	<.001	.64
MINT	14.9 (0.4)	11.2 (4.1)	13.2 (2.9)	<.001	**<.001**
HVLT – Immediate	24.2 (3.9)	9.6 (4.9)	10.2 (4.9)	<.001	.64
HVLT – Delay	9.4 (1.7)	0.9 (1.6)	1.9 (2.1)	<.001	**<.001**
HVLT – Recognition	11.7 (0.4)	5.8 (3.1)	7.6 (2.1)	<.001	**<.001**
Noise Pareidolia – Correct Faces	6.9 (0.4)	6.0 (1.4)	5.9 (1.4)	<.001	.79
Noise Pareidolia – Correct Noise	12.7 (0.8)	11.7 (1.8)	9.0 (3.7)	<.001	**<.001**
Noise Pareidolia – Total Correct	19.6 (1.0)	17.3 (3.1)	15.4 (4.3)	<.001	**<.001**
Noise Pareidolia – Total Pareidolia	0.3 (0.7)	2.2 (2.9)	4.0 (3.9)	<.001	**<.001**

Mean (SD)

KEY: UDS=Uniform Data Set; LBD-MOD=Dementia with Lewy Bodies Module; AD=Alzheimer's disease; DLB=Dementia with Lewy bodies; MoCA=Montreal Cognitive Assessment; MINT=Multilingual Naming Test; HVLT=Hopkins Verbal Learning Test

Bold indicates post-hoc significance for AD vs DLB after correction for multiple comparisons (corrected p-value <.004)

Table 8:

Comparison of UDS and LBD-MOD Measures to Distinguish MCI due to AD from MCI due to DLB

Variable	MCI-AD n=79	MCI-DLB n=22	p-value
Age, y	73.5 (8.8)	75.3 (5.3)	.37
Sex, %M	51.9	68.7	.17
Education, y	15.9 (2.6)	17.0 (2.0)	.09
Hachinski	0.7 (0.8)	0.7 (0.9)	.74
FAQ	2.6 (3.6)	3.4 (4.8)	.42
NPI	4.3 (3.9)	6.3 (5.9)	.06
Depression, %	28.8	64.3	.01
Depression, Total	0.4 (0.7)	1.1 (0.9)	**.004**
Anxiety, %	18.6	46.7	.02
Anxiety, Total	0.2 (0.5)	0.7 (0.8)	**.005**
Apathy, %	27.1	46.7	.14
Apathy, Total	0.4 (0.7)	0.8 (1.0)	.09
CDR	0.5 (0.1)	0.6 (0.3)	.10
CDR-SB	1.3 (0.9)	1.9 (1.4)	.02
Memory	0.5 (0.10	0.5 (0.1)	1.0
Orientation	0.1 (0.3)	0.2 (0.3)	.39
Judgment/Problem Solving	0.4 (0.3)	0.5 (0.3)	.04
Community Affairs	0.1 (0.2)	0.3 (0.4)	.009
Home & Hobbies	0.1 (0.2)	0.2 (0.3)	.27
Personal Care	0.0 (0.2)	0.2 (0.4)	.04
UPDRS	3.0 (3.9)	14.9 (11.6)	**<.001**
Hoehn & Yahr	0.1 (0.5)	1.5 (1.2)	**<.001**
Total Autonomic Features	3.1 (2.5)	5.6 (3.2)	**<.001**
Dysphagia, %	5.3	19.0	.04
Decrease libido, %	22.4	42.9	.06
Decrease sexual performance, %	25.0	52.4	.02
Double vision, %	2.6	19.0	.006
Constipation, %	21.1	61.9	**<.001**
Obstipation, %	14.5	42.9	**.004**
Incomplete emptying of bladder, %	19.7	38.1	.08
Lightheaded with change in position, %	17.1	33.3	.10
Lightheaded with prolonged standing, %	6.6	19.0	.08
Fainting, %	2.6	14.3	.03
Mayo Fluctuations	0.8 (0.9)	1.7 (1.1)	**<.001**
Mayo Sleep RBD, %	22.1	38.1	.14
SCOPA-Sleep Daytime Sleepiness	3.6 (3.0)	3.3 (2.9)	.73
Trailmaking A, seconds	34.7 (11.6)	45.1 (22.1)	**.003**

Variable	MCI-AD n=79	MCI-DLB n=22	p-value
Trailmaking B, seconds	92.5 (40.1)	126.9 (41.2)	**.001**
Noise Pareidolia – Correct Faces	6.8 (0.3)	6.5 (1.1)	.01
Noise Pareidolia – Correct Noise	12.2 (1.6)	11.0 (2.3)	.02
Noise Pareidolia – Total Correct	19.2 (1.6)	17.7 (2.5)	**.001**
Noise Pareidolia – Total Pareidolia	0.7 (1.5)	1.9 (2.2)	**.005**

Mean (SD) or %

KEY: UDS=Uniform Data Set; LBD-MOD=Dementia with Lewy Bodies Module; MCI-AD=mild cognitive impairment due to Alzheimer's disease; MCI-DLB=mild cognitive impairment due to dementia with Lewy bodies; FAQ=Functional Activities Questionnaire; NPI=Neuropsychiatric Inventory; CDR=Clinical Dementia Rating; CDR-SB=CDR Sum of boxes; UPDRS=Unified Parkinson's Disease Rating Scale; RBD=Rapid eye movement sleep behavioral disorder; SCOPA= Scales for Outcomes in Parkinson's disease

Bold indicates significance after correction for multiple comparisons (corrected p-value<.006)

Table 9:

Alignment of Classification of the LBD-MOD with the Lewy Body Composite Risk Score

LBCRS Variable	Controls (n=53)	AD (n=78)	DLB (n=110)	Overall p-value	Post-hoc AD vs DLB	MCI-AD (n=79)	MCI-DLB (n=22)	p-value
Bradykinesia, %	11.1	33.3	98.6	<.001	**<.001**	17.2	73.3	**<.001**
Rigidity, %	2.2	7.1	38.9	<.001	**<.001**	5.2	26.7	.01
Postural Instability, %	11.1	26.2	69.4	<.001	**<.001**	19.0	46.7	.03
Rest Tremor, %	2.2	2.4	27.8	<.001	**<.001**	3.4	26.7	**.004**
Daytime Sleepiness, %	22.2	54.8	80.6	<.001	**<.001**	37.9	66.7	.05
Illogical Thoughts, %	6.7	31.7	75.0	<.001	**<.001**	8.6	26.7	.06
Staring, %	2.3	19.0	60.6	<.001	**<.001**	12.1	33.3	.05
Hallucinations, %	0.0	0.0	47.9	<.001	**<.001**	0.0	6.7	.05
RBD, %	15.6	21.4	61.1	<.001	**<.001**	12.1	26.7	.16
Orthostatic, %	11.1	7.1	36.1	<.001	**<.001**	1.7	13.3	.04
Total, Mean (SD)	0.8 (1.2)	1.9 (1.2)	60. (1.7)	<.001	**<.001**	1.2 (1.1)	3.8 (1.4)	**<.001**

Mean (SD) or %

KEY: LBD-MOD=Dementia with Lewy Bodies Module; LBCRS=Lewy body composite risk score; AD=Alzheimer's disease; DLB=Dementia with Lewy bodies; MCI-AD=mild cognitive impairment due to Alzheimer's disease; MCI-DLB=mild cognitive impairment due to dementia with Lewy bodies; RBD=Rapid eye movement sleep behavioral disorder

Bold indicates post-hoc significance after correction for multiple comparisons (corrected p-value<.005)