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Fluctuations in Cognition and Alertness Vary Independently in Dementia with Lewy Bodies

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Abstract

Background—Fluctuations in mental status are one of the core diagnostic criteria for Dementia with Lewy Bodies (DLB) and are thought to reflect variability in daytime alertness. Previous attempts to study fluctuations have been limited to caregiver reports, observer rating scales, short segments of electroencephalography, or motor-dependent, reaction time tests. Concordance among such measures is often poor, and fluctuations remain difficult to quantify.

Methods—We compared fluctuations in cognition and alertness in patients with DLB (n = 13) and idiopathic Parkinson's Disease (n = 64), a condition associated with deficits in daytime alertness. We systematically and repeatedly collected cognitive and physiologic measures during a 48-hour inpatient protocol in a sound-attenuated sleep laboratory in a geriatric hospital. Cognitive fluctuations were analyzed using coefficients of variation (COVs) derived from performance on a bedside examination familiar to clinicians (digit span). Alertness fluctuations were assessed objectively using COVs from the polysomnographically-based Maintenance of Wakefulness Test.

Results—Despite predictably lower mean digit span performances, DLB patients demonstrated significantly greater cognitive fluctuations than PD patients (p <.001), even when groups were matched on general cognitive impairment. There were no group differences in alertness fluctuations, although DLB patients were less alert than PD patients not receiving dopaminergics.

Conclusions—The prevailing assumption that fluctuations in cognition in DLB are reflected in fluctuations in daytime alertness was not supported by objective, physiological measurements.

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Fluctuating mental status in DLB patients can be detected with repeated administration of a simple bedside exam that can be adapted to a clinic setting.

Keywords

Dementia with Lewy Bodies; fluctuations; cognition; alertness; digit span

INTRODUCTION

Fluctuations are one of the core criteria for Dementia with Lewy Bodies (DLB) and are conceptualized as involving pronounced variation in alertness and cognition [1, 2]. Studies that have examined fluctuations in cognition in such patients typically have operationalized fluctuations by either caregiver/clinician based questionnaires and/or ratings [3–7], or more objectively by motor-dependent, reaction time tests. Such tests are often derived from proprietary pharmaceutical testing programs [8–12], and they can be challenging to administer across a broad range of synucleinopathic patients, because of well-known motor deficits in both simple and choice reaction time characterizing Parkinsonian patients [13]. Considerations such as these make it difficult to integrate objective measurements of fluctuating cognition into routine clinical practice.

In this study, we examined within-patient fluctuations in cognition in DLB patients over a period of 48 hours using a simple, verbally administered, bedside protocol (digit span) not affected by slow manual dexterity. Because the construct of fluctuating mental status implicitly and explicitly has invoked the notion that varying levels of alertness parallel those fluctuations in cognition [5, 7, 11, 12, 14], we used the Maintenance of Wakefulness Test (MWT) as an objective, physiological measure of alertness. As a comparison group, we also examined such fluctuations in another patient group known to incur deficits in daytime alertness, idiopathic Parkinson's Disease (PD).

METHODS

Patients

DLB patients (n=13) met consensually agreed upon criteria from the Third International Consensus conference for the disorder [1]. A detailed presentation of Central, Core, Suggestive and Supportive Features for the patients is shown in Table 1. PD patients (n=64) demonstrated at least two of the cardinal signs for PD diagnosis including bradykinesia, rigidity, resting tremor, and postural instability [16, 17]. None of the PD patients were demented. Twelve had Mini-Mental State Exam (MMSE) [18] scores of less than 28 (n=6 with less than 27) (range 23–27), and four of these had some mild memory complaints, but a formal diagnosis of Mild Cognitive Impairment was not rendered in these patients. MMSE scores of less than 26 are occasionally encountered in PD patients without dementia [19]. We examined separately the subgroup of PD patients with low MMSE scores in our case-control analysis (see below).

Demographic, clinical, and medication information for both the DLB and PD patients are presented in Table 2. There was no difference in benzodiazepine use. Relative to DLB patients, a larger proportion of PD patients used dopamine agonists, although there were no differences in the proportion using levodopa. Levodopa dosage was higher in the PD patients. Usage of anti-psychotics and cholinesterase inhibitors was higher in DLB patients. Fourteen PD patients used neither levodopa nor dopamine agonists. A board-certified neurologist rated each patient's parkinsonism with the Unified Parkinson's Disease Rating Scale (UPDRS) motor subscale [16]. Dose equivalence for those patients taking dopaminergic medications followed standard conversions [20]. Approximately half (62%) of

the DLB patients, but only two of the PD patients, received cholinesterase inhibitors. Only one patient (PD) used stimulant medication, and 14 PD patients were not taking any dopaminergics. All patients completed the Epworth Sleepiness Scale (ESS) [21]; for several of the DLB patients, caregivers assisted in the completion of this scale.

Patients were recruited from the Movement Disorders Clinic at Emory University School of Medicine in Atlanta, Georgia. Advertisements were placed in waiting rooms and in physicians' offices. Any patient interested in participating was contacted by the first author (DB) who provided details and arranged scheduling. Exclusion criteria included serious medical co-morbidities (e.g., history of stroke, myocardial infarction, active cancer, uncontrolled diabetes), history of CNS trauma or infection, history of neurosurgical intervention (pallidotomy, sub-thalamic deep brain stimulation), or current or lifetime Axis I psychiatric diagnosis.

Data collection occurred between March 2008 and May 2012 in a sound-attenuated laboratory at Wesley Woods Geriatric Hospital in Atlanta, Georgia (US). All patients provided written Informed Consent at the beginning of the study. The protocol conformed to the ethical standards of the Declaration of Helsinki for protection of human subjects and was approved by the Institutional Review Board at Emory University.

Bedside verbally administered cognitive testing

We employed digit span forwards and backwards as brief assessments of cognitive fluctuations. These were performed immediately prior to each MWT trial (Fig. 1) (maximum = eight trials per patient). The digit span administration protocol was similar to that used in standard intelligence testing, except that the order of digits varied across trials. In the forwards condition, the technician read a string of digits aloud (e.g., two–nine–six–one) and the patient was asked to repeat these aloud in the order presented. If the patient was able to do this correctly, an additional digit was added to the sequence. Each number of digit strings was presented twice and the particular trial was discontinued when the patient made errors on two consecutive presentations. Following digit span forwards testing, the patient was instructed to repeat a string of digits backwards (e.g., in the above case, one–six–nine–two). The backwards recall always began with a two-digit practice sequence to ensure that patients understood the procedure. All patients were able to do at least two digits backwards when presented initially. The score for digit span was the highest number of digits successfully recalled prior to first error, calculated separately for forwards, for backwards, and for the sum of forwards and backwards. These scores were calculated separately for each of the eight trials.

Physiologic alertness testing

Patients were given the MWT during which they were asked to recline in bed (head elevated) in a darkened room and were instructed to try to remain awake [22]. Each trial of the test lasted 40 minutes and these were evenly spaced throughout the daytime hours for a total of eight over the 48-hour period. For each MWT trial, we generated two measurements: the time (in minutes) to the first 30-second epoch of sleep (Sleep Latency) and the proportion of the 40-minute nap opportunity in which the patient was asleep (Sleep Efficiency). A full description of the procedure is described elsewhere [23]. Using a similar procedure, a mean Sleep Latency of 32.6 minutes has been reported in normal subjects [24].

Clinical fluctuations scale

A subset of patient caregivers/spouses of the patients (n=58) completed this previously published scale [5]. Initially, the scale contained 19 items but the original validation suggested that four items that related to alertness were most sensitive to differentiating DLB

[5]. For the current analyses we examined these originally described four items, but selected six additional items (one, two, thirteen through sixteen) that specifically asked caregivers about fluctuations in cognition. We analyzed the original four items ("alertness" subscale) and the six additional items ("cognitive" subscale) separately.

Inpatient (laboratory) procedures

During the 48-hour protocol (Fig. 1), patients maintained their typical schedule for meals, medications, and nocturnal sleep. They were not kept in time isolation. One patient was studied at a time, usually beginning on Thursday night and ending late Saturday afternoon. To ensure the absence of inadvertent sleep that would compromise the validity of our physiological measurements, patients underwent constant behavioral monitoring, both directly and with infrared video monitoring from an adjacent room, by one of two research technologists who monitored only that patient around the clock. Video monitoring continued during overnight polysomnography. Sleep was prohibited during the daytime, except during MWT trials. Patients were allowed anywhere in the 1,400 square foot laboratory during the 48-hour period but otherwise remained sequestered. They were not allowed to consume caffeinated beverages. Between testing procedures, patients watched television, browsed the Internet, used the telephone, and read magazines. The protocol included two consecutive nights of overnight polysomnography; some of these results have been reported elsewhere [23, 25] but, in brief, nocturnal polysomnography measures were unrelated to the measures of cognitive fluctuations described below. Some patients ($n_{PD} = 9$, $n_{DLB} = 2$) completed fewer than eight testing trials (e.g., leaving for social engagements or were only able to schedule a single day), but exclusion of these patients did not change the major results.

Statistical analysis

Comparisons between DLB and PD patients were made using chi-square tests for categorical variables (or Fisher's exact test, when expected cell frequencies were less than 5) and t-tests for continuous measures. We used Levene's test correction for unequal variances when necessary, and as an additional check, we performed nonparametric Mann-Whitney U tests. For the digit span and MWT data, we characterized each patient by their mean level of performance averaged across all trials, but the main outcome measure was the assessment of intra-individual variability in performance. We accomplished the latter by calculating for each patient a coefficient of variation (COV), which divided each patient's standard deviation by their mean. This ratio expresses variance after accounting for differences in a patient's mean score. The COV allowed comparison of DLB and PD patients on measures for which their average level of performance may differ (e.g., digit span). Additionally, we performed several case control sub-analyses by matching PD and DLB cases on general cognitive ability (MMSE) or age and repeated the COV analysis. We also compared the 14 PD patients not receiving dopaminergics to the 13 DLB patients on COV measures. Spearman's rho was used to examine correlations between objective measures of fluctuations (digit span, MWT) and caregiver-assessments of fluctuations, as well as dopaminergic dose equivalents. In cases with missing data, analyses are reported based on existing data. Statistical significance was determined using an alpha level of 0.05.

RESULTS

Analyses of mean levels

Mean level comparisons between DLB and PD groups are included in Table 3. As would be expected, DLB patients performed more poorly relative to PD patients on both digits forwards and backwards, and, by definition, on the sum of forwards + backwards. There were no differences in cognition or alertness between DLB patients receiving or not receiving cholinesterase inhibitors. Mean levels of alertness derived from the MWT did not

differentiate the two groups (Table 3), however, DLB patients fell asleep more rapidly than the 14 PD patients not taking dopaminergics (t = 2.13, p = .04). Mean levels of caregiver reported fluctuations on the alertness subscale did not significantly distinguish the groups, but caregiver reported fluctuations on the cognition subscale were significantly higher in the DLB patients relative to the PD patients (Table 3).

Analyses of objectively measured fluctuations

The primary goal of this study was to compare objectively measured cognitive fluctuations between groups. COVs of digit span forwards, backwards, and the sum of digits forwards + backwards were significantly higher (t-tests using Levene's adjustment, when appropriate) in DLB patients relative to the PD patients (Table 3). The digit span COV group differences were significant with nonparametric Mann-Whitney U tests as well (forward: p=.003, backward: p=.017, combined: p<.001). A group difference also was seen when digit span performance was expressed more simply as the maximal intra-individual difference between the highest and lowest number of digits (i.e., the range) recalled correctly by a given patient during the 48-hour protocol. So, for example, for digits backwards, 10/13 DLB patients showed a best minus worse difference of three digits, whereas for the PD patients only 26/64 showed a difference of that magnitude (χ^2=5.72, p=0.02). This suggests that a relatively basic, easily computed metric for performance fluctuations may be of value.

Because the PD and DLB groups differed in age, we matched 13 PD patients to the 13 DLB patients on the basis of age and sex. Results were similar. Comparisons between the 14 PD patients not receiving any dopaminergics and the 13 DLB patients also showed parallel findings. Specific comparisons between those using versus not using all other medication classes in Table 2 indicated no significant effect for digit span COV measures to be higher or lower for those using medication within either patient group. Dopaminergic dose equivalents were unrelated to all digit span COV measures for PD and DLB patients taking this drug class. Taken together, these results indicate that medication usage did not account for the differences in cognitive fluctuations.

Although intra-individual differences in cognition existed within this sample, intra-individual variability in physiologically measured alertness (MWT) was similar between patient groups. Using correlational analyses, no associations existed between MWT-derived COV and digit-span derived COV within PD, DLB, or both groups combined (all p's>0.17), further indicating that fluctuations in alertness cannot be equated with fluctuations in cognition, at least within these patient groups. Within PD patients only, those not receiving dopaminergics showed higher MWT-defined COV in sleep efficiency than those receiving dopaminergics, suggesting that use of this medication class may "smooth" daytime alertness to some degree (mean [SD] MWT COV for patients [n = 50] using dopaminergics = .81 [.60] vs mean [SD] MWT COV for patients [n = 14] not using dopaminergics = 1.56 [.80]; t = 3.84, p < .001).

Because some of the PD patients showed mild cognitive impairments, we examined group differences in COVs comparing the 13 DLB patients to the 6 PD patients who had MMSE scores ≤ 26 (M=24.3). Despite also being statistically similar in age, UPDRS, and gender (all ps>.10), the DLB patients still demonstrated significantly greater COVs for digit span combined (p=.002), digits forward (p=.04), and digits backward (p=.004). The DLB and PD subgroup did not differ on MWT COVs (Sleep Latency, p=.60, or Sleep Efficiency, p=.99). Results were similar when comparing the 13 DLB patients to the 12 PD patients who had MMSE scores ≤ 27.

Associations between objectively measured cognitive fluctuations and caregiver-reported fluctuations

Scores from the four-item alertness subscale on the caregiver questionnaire were unrelated to all COV measures of digit span performance, however, scores on the six-item cognitive subscale were related to the COV of the sum of digits forward + backwards (rho=0.33, p=0.01). These data suggested at least partial validation of caregiver's report of cognitive fluctuations with objective measurements made in the inpatient setting.

DISCUSSION

Our data demonstrated that fluctuations in cognition were indeed a distinguishing feature of DLB, but that those fluctuations are independent from alertness, at least when the latter is measured with the MWT. The simple digit span procedure, when administered repeatedly, proved quite sensitive to fluctuations. Although representing a core feature of the condition [1], operationalization of fluctuations in mental status in DLB patients has been inconsistent across research studies [15, 26] and probably remains even more so in clinical practice. Ratings made by others, including caregivers [5] or by clinicians [7, 11] presumably provide data integrating the more long-term experiences [3] of those closest to patients, but the caregiver scale used here was only modestly related to COVs of objective measures of cognitive fluctuations. Previous reaction time studies [9, 11, 12, 27] analyzing COVs on a second-to-second basis often have been used to define fluctuations, however, their duration of administration (typically 90 seconds) provides only the narrowest of temporal windows on a phenomenon that is probably far less circumscribed, especially when compared to caregivers' cumulative experiences of the identified patient's fluctuating cognition over much longer intervals of time. By way of example, time of day in such studies is often left unspecified, though one study noted that all testing occurred between 10:00–11:00 AM [9], thus emphasizing the possibility that some variability across the remainder of the day might have been missed. Reaction time studies involving DLB patients have also typically [11, 12], but not always [10], excluded patients with frank motor impairments who could not perform such tests, thus limiting their relevance for testing trial-to-trial cognitive fluctuations in patients with bradykinesia, rigidity, or tremor. For all these reasons, we believe that repeated administration of a simple, verbally administered bedside exam (i.e., digit span), could hold considerable practical relevance. Although digit span performance may be less influenced by slowed manual reaction time, it may nonetheless reflect a more generalized bradyphrenia, reflecting impairment and slower processing of recent verbally presented material, a phenomenon recognized in Parkinsonian patients [28].

Fluctuations in alertness form a cornerstone of current conceptualizations of variability in cognition in DLB [1, 4, 14]. Our data suggest that the two phenomena may be different. Using Likert scale ratings, Escandon and colleagues [4] also suggested that cognitive fluctuations in dementia were independent from rated levels of alertness, but repetitive measures of cognition or alertness were not performed in that study. Prior attempts to measure fluctuations physiologically with spontaneous electroencephalographic (EEG) activity examined variability of delta band spectral power over a limited 1-hour window at unspecified times of day [7, 11, 12, 29]. These data indicated dampened levels of alertness in DLB patients at a single interval of time but did not speak to variability in those levels of alertness across the entirety of daytime hours as a correlate of fluctuating mental status. We did not perform spectral analyses of the EEG across the daytime hours in our study, which leaves open the possibility that some intra-subject variability might have been missed.

Because the differential diagnosis of DLB using clinical criteria continues to present challenges [2, 15, 30, 31], even for astute clinicians, our findings of a simple-to-administer measure of cognitive fluctuations may bear relevance upon important diagnostic issues of

determination of intra-patient variability. The greatest relevance of the variability data may be the potential for the differentiation of DLB from other types of dementia, such as Alzheimer's disease (AD). Our protocol did not include AD patients, who might have been expected to show reduced variability in cognition relative to the DLB patients. Future work would be required to confirm the utility of this approach in other forms of dementia.

Our study has several weaknesses. In addition to the aforementioned lack of testing in AD patients, perhaps the group for whom presumed lack of variability in cognition might be the most important factor for differential diagnosis, our PD and DLB groups differed in several respects. The PD patients were considerably younger than the DLB patients and this might have influenced our findings, although the sub-analyses of age- and sex-matched PD patients showed similar results both for COVs based on Digit Span and for MWT. Although usage of levodopa was no more common in PD relative to DLB patients, the levodopa dosage equivalent was higher in the PD patients. Interestingly, although use of dopaminergics did not impact measures of fluctuations in cognition, they may have served to "smooth" out fluctuations in alertness seen in untreated PD, perhaps, as we have shown elsewhere [23] by making patients sleepier. DLB patients did not show this effect, but our small sample size (reflecting the intensive nature of the protocol) and relatively low power for within DLB analyses may have worked against detecting such medication effects. Similarly, although cholinesterase inhibitors are associated with improvement in reaction time and attention tasks in DLB [32], we could not demonstrate any corresponding effects on fluctuations here.

These data were collected under the unique conditions of an intensive, 48-hour inpatient protocol with careful and continuous behavioral monitoring. Mega and colleagues [30] proposed that a five-point fluctuation in total MMSE score over an interval of six months would constitute evidence of substantial fluctuation. Our data suggest that substantial variability was present over two consecutive days. Certainly some repetitive sampling of cognition could be performed in clinic setting on a single day, though individual clinics would need to determine how many repetitive administrations over how short a time interval would be a) tolerable to patients and their families; b) amenable to adequate staffing; and c) yield data on intra-individual performance of comparable validity to what we have proposed here. It also is possible that technology transfer (e.g., smartphone applications for repeated verbal administration of digit span) might even be used by caregivers at home, many of whom are deeply involved in acquiring an accurate diagnosis and appropriate treatment for the patients under their care.

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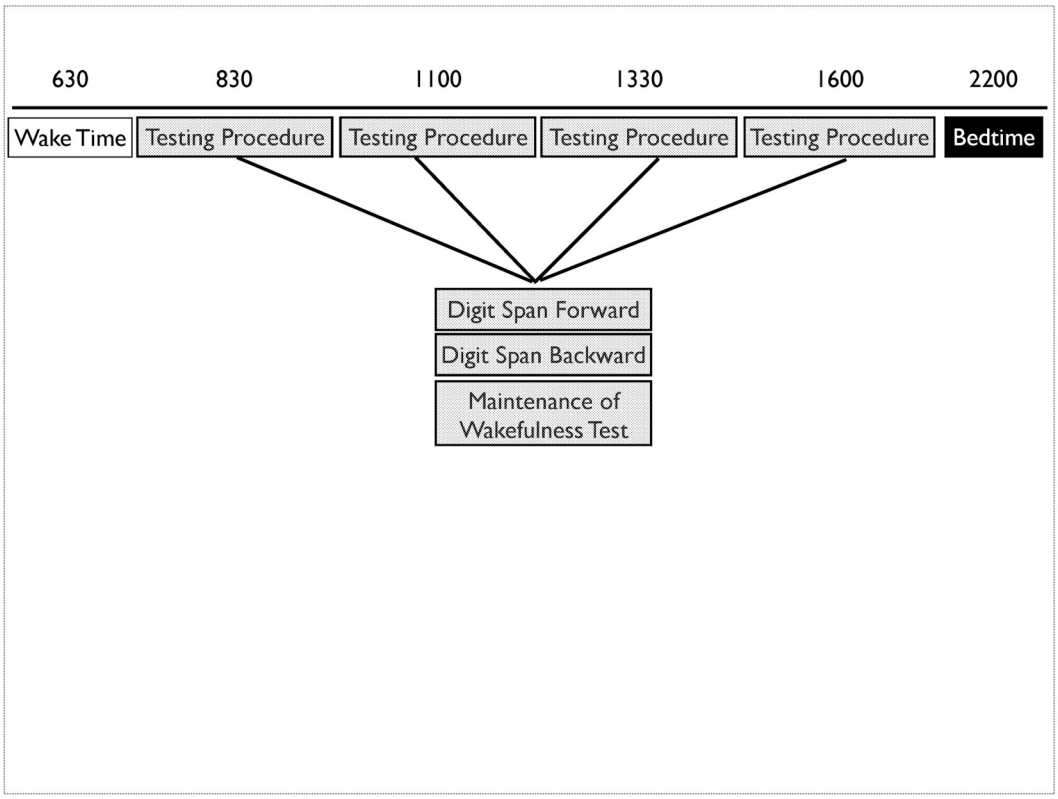

Figure 1.
Example of testing sequence during each day of the 48-hour protocol.

Table 1

Clinical Characteristics of DLB Patients (*n* = 13).

	FEATURES					
Demographics	**Central**	**Core**	**Suggestive**	**Supportive**	**Imaging**	**Temporality**
79 M	+	VH, P	RBD−, NS NA	G, D, S	Non-focal atrophy	Preceding
73 M	+	FC, VH, P	RBD+, NS NA	U	Non-focal atrophy	Concurrent
58 M	+	VH, P	RBD+, NS NA	D	Non-focal atrophy	Preceding
69 M	+	VH, P	RBD−, NS+	G, D, DL	Non-focal atrophy	Preceding
72 M	+	FC, VH, P	RBD−, NS NA	G, D, S	Non-focal atrophy	Preceding
74 M	+	FC, VH, P	RBD−, NS NA	G, S, DL	Non-focal atrophy, WMH	Concurrent
69 M	+	VH, P	RBD+, NS NA	D, U, S	WNL	Concurrent
79 M	+	P	RBD+, NS+	D	Non-focal atrophy	Concurrent
71 M	+	VH, P	RBD+, NS−	D, U	Non-focal atrophy	Preceding
71 M	+	VH, P	RBD−, NS NA	EEG	Non-focal atrophy	Preceding
73 F	+	P	RBD−, NS−	D, U, G	Non-focal atrophy	Concurrent
69 M	+	VH, P	RBD+, NS−	D, G, S	NA	Concurrent
59 M	+	FC, P	RBD+, NS NA	EEG	WMH	Preceding

NOTES (following criteria shown in ref [1]**): Demographics** shown as Age (in years) and Sex (male, M or female, F); **Central Features** are progressive cognitive declines characterized as persistent memory loss and/or deficits in attention, executive function or visuo-spatial ability (indicated by +/−); **Core Features** are defined as presence (when indicated) of fluctuating cognition (FC), visual hallucinations (VH) or Parkinsonian motor features (P); **Suggestive Features** are defined as Rapid Eye Movement Behavior Disorder (RBD: indicated by +/−) or Neuroleptic Sensitivity (NS: indicated by +/− or not applicable [neuroleptics not used]); (Low dopamine transporter uptake was not included in the table as it was not used routinely in our Center); **Supportive Features** are defined as abnormalities of gait/balance (G), depression (D), urinary symptoms (U), EEG (electroencephalographically assessed slowing), syncope (S), delusions (DL); **Imaging** defined as MRI findings indicating non-focal findings characterized by atrophy, diffuse white matter hyperintensities (WMH), findings considered within normal limits (WNL), or not available (NA); and **Temporality,** defined as cognitive decline preceding motor impairment (Preceding) or occurring simultaneously with motor impairment (Concurrent).

Table 2

Demographics and clinical data (mean, SD) for Parkinson's disease (n = 64) and Dementia with Lewy Bodies (n = 13) patients.

	Parkinson's Disease	**Dementia with Lewy Bodies**	***p* value**
Age	62.95 (9.70)	70.46 (6.24)	0.009
Gender (% male)	66%	92%	0.06
ESS	10.25 (4.44)	10.88 (5.21)	0.65
MMSE	28.55 (1.73)	22.85 (4.62)	0.001
UPDRS	17.56 (8.91)	26.40 (11.38)	0.008
Disease duration (years)	5.57 (3.95)	4.08 (3.54)	0.22
Levodopa dosage equivalent (mg)	460.22 (379.62)	233.35 (276.63)	0.045
Medication Usage (N, % using)			
Levodopa	42 (65.6)	7 (53.8)	0.42
Dopamine agonists	35 (54.7)	1 (7.7)	0.002
Benzodiazepines, GABAergic site-specific agonists	9 (14.1)	2 (15.4)	0.99
Cholinesterase inhibitors	2 (3.1)	8 (61.5)	0.0001
Anti-psychotics	0 (0%)	6 (46.2)	0.0001
Anti-depressants	22 (34.4)	8 (61.5)	0.067
MAO-B inhibitors	18 (28.1)	1 (7.7)	0.17

NOTES: ESS = Epworth Sleepiness Scale; MMSE = Mini-Mental State Exam; UPDRS = Unified Parkinson's Disease Rating Scale (motor subscale). Total N's slightly lower for some variables: ESS (n = 76); MMSE (n = 73); UPDRS (n = 65); and disease duration (n = 74).

Table 3

Mean values and coefficients of variation (COV) for Parkinson's disease and Dementia with Lewy Bodies patients. Standard deviations are in parentheses. Comparisons used t-tests with Levene's adjustment when variances were unequal.

	Parkinson's Disease	Dementia with Lewy Bodies	*p* value
Digit Span			
Mean Digits Forward	6.24 (0.85)	4.90 (0.97)	<0.001
Mean Digits Backward	4.09 (1.11)	2.63 (0.99)	<0.001
Mean Digits Forwards + Backwards	10.29 (1.79)	7.53 (1.70)	<0.001
COV Digits Forward	0.13 (0.05)	0.27 (0.20)	0.02
COV Digits Backward	0.32 (0.19)	0.64 (0.43)	0.02
COV Digits Forwards + Backwards	0.15 (0.09)	0.25 (0.08)	<0.001
Maintenance of Wakefulness Test			
Mean Sleep Latency (mins)	18.39 (12.68)	18.42 (15.17)	0.99
Mean Sleep Efficiency (%)	28.11 (23.41)	27.29 (28.70)	0.92
COV Sleep Latency	0.65 (0.37)	0.75 (0.62)	0.59
COV Sleep Efficiency	0.97 (0.71)	0.83 (0.82)	0.53
Caregiver Fluctuations Scale			
Alertness Subscale	0.74 (0.95)	1.33 (0.89)	0.06
Cognitive Subscale	1.61 (1.90)	4.25 (1.06)	<0.001