Published in final edited form as:

Alzheimers Dement. 2014 March ; 10(2): 171–178. doi:10.1016/j.jalz.2013.04.003.

Accounting for Functional Loss in Alzheimer's Disease and Dementia with Lewy Bodies: Beyond Cognition

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Abstract

Background—The relative contributions of cognitive, motor and behavioral deficits to the impairment of physical or instrumental activities of daily living (ADL) may differ in patients with Dementia with Lewy Bodies (DLB) and Alzheimer's Disease (AD).

Methods—Multiple linear regression analyses were used to identify the amount of variability in physical self-maintenance and instrumental ADL ratings predicted by cognitive, motor, and behavioral indices separately for patients with autopsy-diagnosed DLB (n=39) or AD (n=39).

Results—Motor dysfunction accounted for significant variance in physical ADL in DLB (R^2 change=0.17), whereas behavioral (R^2 change=0.23) and motor dysfunction (R^2 change=0.13) accounted for significant variance in AD. Motor (R^2 change=0.32) and cognitive (R^2 change=0.10) dysfunction accounted for significant variance in instrumental ADL in DLB, whereas cognitive (R^2 change=0.36) and behavioral (R^2 change=0.12) dysfunction accounted for significant variance in AD.

Conclusion—Cognitive, motor, and behavioral deficits contribute differently to ADL changes in DLB and AD. Thus, treatments designed to ameliorate a certain aspect of AD or DLB (e.g., cognitive dysfunction) may have a larger impact on everyday function in one disorder than the other.

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Keywords

Dementia with Lewy Bodies; Alzheimer's Disease; Activities of Daily Living; Cognition; Behavior; Motor Function

1. Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by progressive decline in memory and other cognitive abilities that arises from atrophy, synapse loss, and accumulation of amyloidogenic plaques and neurofibrillary tangles in limbic and neocortical brain regions. Cognitive decline in AD is often accompanied by behavioral changes such as depression, apathy, agitation or disinhibition [1], and in some combination these factors lead to profound functional decline with a gradual loss of independence in performing usual activities of daily living (ADL)[2]. Although cognitive impairment is usually viewed as the primary determinant of functional decline in AD, several studies have linked behavioral deficits to disability in physical self-maintenance (bathing, toileting, eating) and instrumental (e.g., financial management, shopping) ADL [3, 4] and particularly rapid loss of functional independence [3–9]. In some cases, the relationship between behavioral deficits and ADL decline is independent of cognitive dysfunction [6, 9, 10].

Dementia with Lewy Bodies (DLB) is the second most common cause of degenerative dementia. DLB is characterized by neuron loss and the accumulation of Lewy bodies in brainstem, limbic, and neocortical structures. In most cases, patients with DLB have concomitant AD pathology in the same limbic and neocortical distribution as in “pure” AD, but the AD pathology is usually less extensive and may be largely limited to neurofibrillary tangles [11]. Given the neuropathologic similarities, it follows that the two disorders share a common clinical presentation and are often difficult to differentiate in life [12]. There are, however, certain clinical features that are more prevalent in DLB than in AD including mild parkinsonism, recurrent and well-formed visual hallucinations, and fluctuations in alertness [12–16]. The two disorders also differ subtly in the pattern of cognitive deficits they engender with DLB patients exhibiting milder memory deficits than comparably demented patients with AD [17–19] but more severe deficits in visuospatial skills, verbal fluency, executive functions, and psychomotor speed [20–23]. Several studies suggest that psychosis and depression are more common in DLB than in AD [24, 25]. Apathy and disinhibition, both thought to be mediated by frontal systems, may present at a milder level of dementia in AD than in DLB [26].

Differences in the clinical characteristics of DLB and AD suggest that unique factors may contribute to decline in physical and instrumental ADL. Understanding the factors that contribute to functional decline is important because treatment designed to ameliorate a certain aspect of AD or DLB (e.g., cognitive dysfunction) may have a larger impact on everyday function in one disorder than the other. Unfortunately, little is known about the relative contributions of the various types of deficits to overall functional impairment in patients with DLB, or about potential differences in the relative importance of factors underlying functional decline in DLB and AD. The present study addressed these issues by retrospectively examining the severity of ADL decline in mildly to moderately demented

patients with autopsy-proven DLB or AD, and comparing the relative contributions of cognitive, motor, and behavioral function to physical and instrumental ADL performance in the two disorders.

2. Methods

2.1 Participants

The present study included clinical data collected from 39 cases of autopsy-confirmed DLB and 39 cases of autopsy-confirmed AD. During life, all were participants at the University of California, San Diego (UCSD) Shiley-Marcos Alzheimer's Disease Research Center (ADRC) between 1986 and 2000. Inclusion criteria included: 1) presence of mild cognitive impairment or dementia; 2) absence of significant pathological process (e.g., infarct with a clinical history of stroke) other than DLB or AD; 3) absence of debilitating medical (e.g., cancer) or psychiatric (e.g., depression) illness; and 4) score of 10 or greater on the Mini Mental State Examination (MMSE). Consecutive cases of DLB adhering to the inclusion criteria were matched to AD cases on the basis of age, education, and MMSE score. When more than one AD patient was an appropriate match, that patient was randomly selected. Because of the matching procedure, there were no significant group differences in age, education, or MMSE scores (all p -values >0.5) (Table 1). On average, duration of illness was slightly longer in AD ($p=0.05$), and death occurred sooner following evaluation in DLB ($p<0.05$). Modified Hachinski scores did not differ ($p>0.8$) and were low in both groups indicating the absence of serious cerebrovascular problems. The majority of participants were followed prior to the development of the clinical criteria for DLB so a clinical diagnosis of DLB was given to only 10/39 DLB patients and 2/39 AD patients. The remaining patients were clinically diagnosed with AD by two senior staff neurologists.

The research protocol was reviewed and approved by the human subjects review board at UCSD. Informed consent to participate in the present investigation was obtained at the point of entry into the longitudinal study from all patients or their caregivers consistent with California State law. Informed consent for autopsy was obtained at the time of death from the next of kin.

2.2 Neuropathologic procedures and comparisons

Autopsy was performed within 12 hours of death using a previously described protocol [27]. Total plaques, neuritic plaques, NFT, and Lewy body counts were determined by the same pathologist (L.A.H). A modified Braak stage was obtained for each case using previously detailed methods [28] (see Table 1). The DLB cases met consensus criteria for the pathologic diagnosis of DLB based on hematoxylin-eosin (H & E) staining and immunostaining with antibodies against ubiquitin [29] and retrospectively for α -synuclein [15]. Cases were only construed as DLB if Lewy bodies were found in the locus ceruleus, substantia nigra, and/or nucleus basalis of Meynert, as well as in the neocortex. Because all cases categorized as DLB had neocortical as well as brainstem Lewy bodies, they fell into either the limbic (transitional) or neocortical categories proposed in the 1996 consensus guidelines for the pathologic diagnosis of DLB [29]. Cases were not classified as DLB if Lewy bodies were only found in the amygdala. Of the cases of DLB, 36 had sufficient

concomitant AD pathology to warrant a secondary diagnosis of AD. Using historical terminology, these cases would have been construed as “Lewy Body Variant of Alzheimer’s Disease.” The neuropathologic diagnosis of AD was based on both NIA-Reagan [30] and Consortium to Establish a Registry for Alzheimer’s Disease criteria [31]. None of the AD cases had Lewy bodies in the neocortex or pigmented brainstem nuclei [32]. No AD case was included if Lewy bodies were found in the amygdala.

2.3 Clinical procedures and measures

All participants had completed annual medical, neurological, psychosocial, and neuropsychological evaluations. Data from the first evaluation were used in the present study. The evaluations included several standardized measures that contributed to the current analyses. In some cases, a derived index was calculated from components of one or several standardized assessment instruments as described below.

2.31 Cognitive impairment index—The severity of global cognitive impairment was measured by the total score on the Mattis Dementia Rating Scale (DRS) [33]. The DRS is a standardized, 144-point mental status examination consisting of 5 subscales that assess Attention (37 points), Initiation/Perseveration (37 points), Construction (6 points), Conceptualization (39 points) and Memory (25 points). Higher scores indicate better performance. The DRS was administered to each patient according to published procedures [33], with the exception that all items were administered to each patient.

2.32 Motor impairment index—A motor index was derived from scores on specific components of the ADRC structured neurological examination [34]. The motor examination of many of the DLB and AD patients occurred prior to the development of the Uniform Parkinson’s Disease Rating Scale (UPDRS) [35] and its implementation at the ADRC, but the vast majority of the rated functions in our derived index overlap that scale (differences are noted below). Specifically, the motor index included a staff neurologist’s dichotomous ratings of the presence (1 point) or absence (0 points) of abnormal finger tapping ability (right, left), abnormal performance of rapid alternating movements (right, left), neck rigidity, arm rigidity (right, left), leg rigidity (right, left), action tremor (right, left), parkinsonian tremor (in the neck or any extremity vs. five separate ratings in the UPDRS), parkinsonian speech, parkinsonian gait, other gait disorder (not in the UPDRS), masked facies, bradykinesia, stooped posture, inability to rise from chair, and postural instability. The motor index score ranged from 0 to 20 with higher scores signifying greater motor abnormality.

2.33 Behavior impairment index—Many of the individuals who were included in this dataset of autopsied cases were evaluated prior to the development of comprehensive neurobehavioral measures [e.g., the Neuropsychiatric Inventory (NPI)]. Therefore, a behavior index was derived from scores on selected items from the Physical Self-Maintenance Scale [36] and the Blessed Functional Scale [37] that best reflect personality disorder often related to frontal lobe dysfunction. Specific behavioral abnormalities were rated as present (1 point) or absent (0 points) based on the report of a well-informed caregiver interviewed by a clinical nurse specialist. The items included in the behavior index

were: 1) takes things from others, 2) bothers people, 3) verbally abusive, 4) mood swings, 5) inappropriate laughter, 6) undresses in public, 7) unmotivated, 8) purposeless hyperactivity, and 9) diminished emotional response. Behavioral index scores ranged from 0 to 9 with higher scores indicating a greater degree of dysfunction.

2.34 Physical self-maintenance activities of daily living (ADL)—Decline in physical self-maintenance ADL was measured by items 1–6 of the Physical Self-Maintenance Scale [36]. These items assess feeding, dressing, toileting, grooming, physical ambulation, and bathing. Each activity is scored on a 1 (performs independently) to 5 (completely dependent on the help of others) point scale based on the report of a well-informed caregiver interviewed by a clinical nurse specialist. Scores ranged from 6 to 30 with higher scores signifying greater impairment.

2.35 Instrumental activities of daily living (IADL)—Decline in IADL was measured by the Pfeffer Outpatient Disability Scale [PODS; [38]]. This scale rates the ability to manage finances, fill out forms, shop, play games of skill, cook, keep abreast of current events, pay attention to a television program or book, remember appointments, and travel outside the neighborhood. Each activity is scored as 0 (performs independently), 1 (needs some assistance), or 2 (completely dependent on the help of others) based on the report of a well-informed caregiver interviewed by a clinical nurse specialist. Scores ranged from 0–20 with higher scores indicative of greater impairment.

2.4 Statistical analyses

Multiple linear regression analyses were used to identify the amount of variability predicted in physical ADL and IADL by the cognitive, motor, and behavioral indices separately for the DLB and AD groups. Data screening identified neither significant deviation from the assumptions of linear regression nor evidence of excessive intercorrelation (i.e., multicollinearity) between the independent predictors. The initial models included age and education, but these demographic characteristics did not hold any additive value and were therefore dropped from the final analyses. The resulting full models took the form: $ADL = \beta_0 + (\beta_1 * \text{Cognition}) + (\beta_2 * \text{Motor}) + (\beta_3 * \text{Behavioral}) + \text{Error}$. Group comparisons of the goodness of fit of the physical ADL and IADL full models were conducted using Fisher's Z Transformation. Finally, best fit models were determined by comparing Mallows' Cp [39] and adjusted R^2 . Mallows' Cp is a function of the error sum of squares for the full model and for the reduced model. Larger Cp values reflect bias in the parameter estimates of the regression equation. A favorable Cp approximates the number of predictor variables, including the constant, in the model. Adjusted R^2 is an index of the amount of variability explained by a model relatively independent of the number of predictor variables in that model. Therefore, the best fit model will have the highest adjusted R^2 in conjunction with the lowest Cp.

3. Results

The average cognitive, motor, behavioral, and functional scores achieved by the DLB and AD patients are shown in Table 2. The DLB and AD groups did not differ significantly on cognitive ($t(76)=1.6, p>0.1$) or behavioral ($t(76)=-0.1, p>0.9$) index scores. As expected,

patients with DLB had a worse motor index score than patients with AD ($t(76)=-2.4$, $p<0.05$). The correlation between cognitive and behavioral (DLB: $r=-.22$, AD: $r=-.39$), cognitive and motor (DLB: $r=-0.25$, AD: $r=-0.30$), and behavioral and motor (DLB: $r=0.28$, AD: $r=0.18$) indices were similar for the two groups. No correlation was robust indicating that the indices were relatively independent of one another. The DLB patients had significantly worse ratings of physical ADL than patients with AD ($t(76)=-2.5$, $p<0.05$); however, the majority of participants in both groups were rated as unimpaired in their ability to perform these basic functions. The groups did not differ significantly in ratings of their ability to perform IADL ($t(76)=-1.6$, $p>0.1$).

3.1 Prediction of decline in physical self-maintenance activities of daily living

Cognitive, motor, and behavioral indices combined accounted for 22% of the variance in physical ADL for the DLB group compared to 38% of the variance in physical ADL for the AD group. The variables predicted basic functioning equally well in each patient group (Fisher Z Transformations; $p=0.3$). Standardized beta coefficients, which provide an estimate of the effect of each predictor variable on the dependent variable (i.e., physical ADL), are presented in the technical appendix (Table 3).

Although the combined indices predicted ratings of physical ADL equally well for the DLB and AD patient groups, the specific variables that contributed significantly to the best fit model differed for the two groups. The motor index alone accounted for 17% of the variance in physical ADL for the patients with DLB [$C_p=2.3$; adjusted $R^2=0.15$; $F(1,37)=7.5$, $p<0.01$]. In contrast, the behavioral index was the strongest predictor of physical ADL in patients with AD, accounting for 23% of the variance. The motor index explained an additional 13% of the variance. Together, the behavioral and motor indices accounted for 36% of the variance in physical ADL for patients with AD [$C_p=3.3$; adjusted $R^2=0.32$; $F(2,36)=10.0$, $p<0.001$]. The technical appendix (Table 4) details the models.

3.2 Prediction of decline in instrumental activities of daily living

Cognitive, motor, and behavioral indices combined accounted for 44% of the variance in IADL in the DLB group and 49% of the variance in IADL in the AD group. The cognitive, motor, and behavioral indices were equally good at predicting variability in IADL in the AD and DLB groups (goodness of fit Fisher Z Transformations; $p > 0.4$). The standardized beta coefficients are presented in the technical appendix (Table 3).

The specific indices that best predicted the ability to complete IADL differed for the DLB and AD groups. For patients with DLB, the motor index best predicted ratings of IADL accounting for 32% of the variance, and the cognitive index significantly improved the model accounting for an additional 10% of the variance. Together these two indices accounted for 42% of the variance in IADL for patients with DLB [$C_p=3.5$; adjusted $R^2=0.38$; $F(2,36)=12.2$, $p<0.001$]. In contrast, the cognitive index was the best predictor of ratings of IADL for the AD group accounting for 36% of the variance with an additional 12% of the variance accounted for by the behavioral index. The cognitive and behavioral indices accounted for 49% of the variance in instrumental ADL for patients with AD [$C_p=2.1$; adjusted $R^2=0.46$; $F(2,36)=17.0$, $p<0.001$].

4. Discussion

The present study set out to: 1) determine if informants' ratings of physical ADL or IADL differ in autopsy-confirmed cases of DLB or AD, and 2) determine if deficits in cognition, motor function, and behavior differentially contribute to ratings of functional decline in these groups. As to the first goal, DLB patients were rated as having greater disability in physical self-maintenance, such as toileting, bathing, and grooming, than AD patients even when dementia was still relatively mild. However, these physical ADL were only marginally impacted and did not likely cause disability in either group. In contrast, complex skills that comprise IADL, such as medication or financial management, were equally impacted by DLB and AD.

Regarding the second goal, the combination of cognitive, motor, and behavioral indices that best predicted physical ADL and IADL ratings differed in the DLB and AD groups. Motor disability was the only variable to predict physical ADL ratings in DLB. In AD, behavioral disturbance had the greatest impact on physical ADL ratings with motor disability significantly improving the model. Motor disability would impact physical ADL that are relatively overlearned, automatic skills dependent on physical strength, agility, and stability for completion. Greater motor disability in DLB than AD may account for the more prominent role it plays in the physical ADL deficits of the DLB patients. Our AD patients were in a mild stage, but a previous study found a relationship between motor disability and everyday functioning in severely affected AD patients [40]. Consistent with several previous studies [3, 4, 9], behavioral disturbance was the best predictor of physical ADL for patients with AD. This may reflect a lack of motivation (i.e., apathy) or focus (i.e., disinhibition) necessary to carry out a task.

The findings with IADL are more complex. In DLB, motor disability best predicted IADL ratings with severity of cognitive impairment adding predictive value. In AD, severity of cognitive impairment predicted IADL ratings with behavioral disturbance improving the model. Because IADL are thought to be cognitively-demanding rather than physically-demanding skills, it is noteworthy that motor disability was associated with IADL in the DLB group. Waite and colleagues [41] suggest that greater levels of motor disability result in greater functional impairment in general. However, motor disability in the DLB patients was relatively mild overall, and the DLB and AD groups did not differ in severity of IADL impairment despite differences in motor disability. Another explanation is that motor disability in DLB serves as a proxy for the general integrity of the basal ganglia, and cognitive impairment associated with basal ganglia dysfunction (e.g., executive dysfunction [17, 42–44]) contributes to the IADL deficits in DLB. Thus, the association between motor disability and IADL in DLB may be tapping an important aspect of cognition not measured by our cognitive index.

As expected, cognitive decline was the strongest predictor of IADL impairment in patients with AD. However, behavioral disturbance added to the model after accounting for cognitive impairment. The importance of behavioral disturbance in the IADL impairment of patients with AD is supported by previous studies [3, 4, 9]. Behavioral disturbance was not an important predictor of physical ADL or IADL in patients with DLB despite an absence of

overall group difference in the behavioral index. Our behavioral index combining ratings of apathy and disinhibition may not tap the most disruptive type of behavioral disturbance in the DLB patients which may be depressive or psychotic in nature.

One limitation of the present study is that the impact of psychotic features or depressive symptoms on decline in everyday functioning was not examined. Psychosis in patients with AD is associated with a rapid decline in behaviors requiring higher-order functional skills [5, 24, 45] independent of cognitive decline [9, 10] and depression [9]. Because the incidence of hallucinations, delusions, and symptoms of depression are generally greater in DLB than in AD [24, 25], future studies are needed to determine how psychotic and depressive symptoms relate to functional decline in DLB. The use of a specific and detailed measure of behavioral symptoms, such as the Neuropsychiatric Inventory (NPI), would have allowed a more comprehensive assessment of the impact of behavioral disturbance on functional decline.

Several additional caveats should be noted. First, the results of the analyses using the physical ADL measure warrant cautious interpretation because both groups were minimally impaired in basic self-maintenance. Ratings of physical ADL are most useful for assessing those with severe dementia [46] and patients with very severe cognitive impairment (MMSE < 10) were excluded from the present study. Despite the limited range of scores, these results are likely reliable because the physical ADL measure was continuous and data did not markedly violate assumptions of linear regression. Second, the study did not address the impact of fluctuations in cognition and alertness on everyday functioning. A previous study suggests that this feature of DLB may contribute to functional decline [47]. Third, the sample is more demographically similar than generally reported because most DLB patients had concomitant AD. However, significant group differences were present indicating that Lewy body pathology made an important contribution to the findings. Finally, the functional assessment relied on informant-based ratings rather than direct observation of a patient's ability to complete ADL. While informant-based ratings are preferred over patient-based ratings, potential biases on the part of the informant may lead to inaccurate estimation of a patient's abilities [46].

Despite these limitations, the results demonstrate that problems in physical self-maintenance are greater in DLB than AD, but are mild in both groups relatively early in the course of disease. Problems with IADL occur early in the course and are equally severe in both disorders. Cognitive, motor, and behavioral deficits make distinct contributions to ADL changes in DLB and AD. Taken together, these results have clinical implications because they suggest that treatment designed to ameliorate a certain aspect of AD or DLB may have a larger impact on everyday function in one disorder than the other.

Acknowledgments

This study was supported by NIH grants NS049298, AG12963, and AG05131 to the University of California, San Diego. We thank the participants and staff of the UCSD Shiley-Marcos Alzheimer's Disease Research Center.

References

1. Aarsland D, Cummings JL, Larsen JP. Neuropsychiatric differences between Parkinson's disease with dementia and Alzheimer's disease. *Int J Geriatr Psychiatry*. 2001; 16:184–91. [PubMed: 11241724]
2. D'Onofrio G, Sancarolo D, Panza F, Copetti M, Cascavilla L, Paris F, et al. Neuropsychiatric symptoms and functional status in Alzheimer's disease and vascular dementia patients. *Curr Alzheimer Res*. 2012; 9:759–71. [PubMed: 22715983]
3. Stout JC, Wyman MF, Johnson SA, Peavy GM, Salmon DP. Frontal behavioral syndromes and functional status in probable Alzheimer disease. *Am J Geriatr Psychiatry*. 2003; 11:683–6. [PubMed: 14609810]
4. Boyle PA, Malloy PF, Salloway S, Cahn-Weiner DA, Cohen R, Cummings JL. Executive dysfunction and apathy predict functional impairment in Alzheimer disease. *Am J Geriatr Psychiatry*. 2003; 11:214–21. [PubMed: 12611751]
5. Stern Y, Hesdorffer D, Sano M, Mayeux R. Measurement and prediction of functional capacity in Alzheimer's disease. *Neurology*. 1990; 40:8–14. [PubMed: 2296387]
6. Fitz AG, Teri L. Depression, cognition, and functional ability in patients with Alzheimer's disease. *J Am Geriatr Soc*. 1994; 42:186–91. [PubMed: 8126334]
7. Harwood DG, Sultzer DL, Wheatley MV. Impaired insight in Alzheimer disease: association with cognitive deficits, psychiatric symptoms, and behavioral disturbances. *Neuropsychiatry Neuropsychol Behav Neurol*. 2000; 13:83–8. [PubMed: 10780626]
8. Tekin S, Fairbanks LA, O'Connor S, Rosenberg S, Cummings JL. Activities of daily living in Alzheimer's disease: neuropsychiatric, cognitive, and medical illness influences. *Am J Geriatr Psychiatry*. 2001; 9:81–6. [PubMed: 11156757]
9. Tran M, Bedard M, Molloy DW, Dubois S, Lever JA. Associations between psychotic symptoms and dependence in activities of daily living among older adults with Alzheimer's disease. *Int Psychogeriatr*. 2003; 15:171–9. [PubMed: 14620075]
10. Harwood DG, Barker WW, Ownby RL, Duara R. Relationship of behavioral and psychological symptoms to cognitive impairment and functional status in Alzheimer's disease. *Int J Geriatr Psychiatry*. 2000; 15:393–400. [PubMed: 10822237]
11. Hansen LA, Masliah E, Galasko D, Terry RD. Plaque-only Alzheimer disease is usually the lewy body variant, and vice versa. *J Neuropathol Exp Neurol*. 1993; 52:648–54. [PubMed: 8229084]
12. Merdes AR, Hansen LA, Jeste DV, Galasko D, Hofstetter CR, Ho GJ, et al. Influence of Alzheimer pathology on clinical diagnostic accuracy in dementia with Lewy bodies. *Neurology*. 2003; 60:1586–90. [PubMed: 12771246]
13. Galasko D, Katzman R, Salmon DP, Hansen L. Clinical and neuropathological findings in Lewy body dementias. *Brain and Cognition*. 1996; 31:166–75. [PubMed: 8811993]
14. Hansen L, Salmon D, Galasko DR, Masliah E, Katzman R, DeTeresa R, et al. The Lewy body variant of Alzheimer's disease: A clinical and pathologic entity. *Neurology*. 1990; 40:1–8. [PubMed: 2153271]
15. McKeith IG, Dickson DW, Lowe J, Emre M, O'Brien JT, Feldman H, et al. Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. *Neurology*. 2005; 65:1863–72. [PubMed: 16237129]
16. Kaur B, Harvey DJ, Decarli CS, Zhang L, Sabbagh MN, Olichney JM. Extrapyramidal Signs by Dementia Severity in Alzheimer Disease and Dementia With Lewy Bodies. *Alzheimer Dis Assoc Disord*. in press.
17. Connor DJ, Salmon DP, Sandy TJ, Galasko D, Hansen LA, Thal LJ. Cognitive profiles of autopsy-confirmed Lewy body variant vs pure Alzheimer disease. *Arch Neurol*. 1998; 55:994–1000. [PubMed: 9678318]
18. Heyman A, Fillenbaum GG, Gearing M, Mirra SS, Welsh-Bohmer KA, Peterson B, et al. Comparison of Lewy body variant of Alzheimer's disease with pure Alzheimer's disease: Consortium to establish a registry for Alzheimer's disease, part XIX. *Neurology*. 1999; 52:1839–44. [PubMed: 10371532]

19. Hamilton JM, Salmon DP, Galasko D, Hansen LA. Distinct memory deficits in dementia with Lewy bodies and Alzheimer's disease. *J Int Neuropsychol Soc.* 2002; 8:209.
20. Tiraboschi P, Salmon DP, Hansen LA, Hofstetter RC, Thal LJ, Corey-Bloom J. What best differentiates Lewy body from Alzheimer's disease in early-stage dementia? *Brain.* 2006; 129:729–35. [PubMed: 16401618]
21. Mosimann UP, Mather G, Wesnes KA, O'Brien JT, Burn DJ, McKeith IG. Visual perception in Parkinson disease dementia and dementia with Lewy bodies. *Neurology.* 2004; 63:2091–6. [PubMed: 15596755]
22. Crowell TA, Luis CA, Cox DE, Mullan M. Neuropsychological comparison of Alzheimer's disease and dementia with lewy bodies. *Dement Geriatr Cogn Disord.* 2007; 23:120–5. [PubMed: 17148939]
23. Hamilton JM, Salmon DP, Galasko D, Raman R, Emond J, Hansen LA, et al. Visuospatial deficits predict rate of cognitive decline in autopsy-verified dementia with Lewy bodies. *Neuropsychology.* 2008; 22:729–37. [PubMed: 18999346]
24. Rockwell E, Choure J, Galasko D, Olichney J, Jeste DV. Psychopathology at initial diagnosis in dementia with Lewy bodies versus Alzheimer disease: comparison of matched groups with autopsy-confirmed diagnoses. *Int J Geriatr Psychiatry.* 2000; 15:819–23. [PubMed: 10984728]
25. Ballard C, Holmes C, McKeith I, Neill D, O'Brien J, Cairns N, et al. Psychiatric morbidity in dementia with Lewy bodies: a prospective clinical and neuropathological comparative study with Alzheimer's disease. *Am J Psychiatry.* 1999; 156:1039–45. [PubMed: 10401449]
26. Peavy G, Salmon DP, Edland SD, Tam S, Hansen LA, Masliah E, et al. Neuropsychiatric Features of Frontal Lobe Dysfunction in Autopsy-Confirmed Patients with Lewy Bodies and "Pure" Alzheimer's Disease. *Am J Geriatr Psychiatry.* In Press.
27. Terry RD, Peck A, DeTeresa R, Schechter R, Horoupian DS. Some morphometric aspects of the brain in senile dementia of the Alzheimer type. *Ann Neurol.* 1981; 10:184–92. [PubMed: 7283403]
28. Hansen L, Samuel W. Criteria for Alzheimer's disease and the nosology of Dementia with Lewy bodies. *Neurology.* 1997; 48:126–32. [PubMed: 9008507]
29. McKeith IG, Galasko D, Kosaka K, Perry EK, Dickson DW, Hansen LA, et al. Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the consortium on DLB international workshop. *Neurology.* 1996; 47:1113–24. [PubMed: 8909416]
30. Hyman BT, Trojanowski JQ. Consensus recommendations for the postmortem diagnosis of Alzheimer disease from the National Institute on Aging and the Reagan Institute Working Group on diagnostic criteria for the neuropathological assessment of Alzheimer disease. *J Neuropathol Exp Neurol.* 1997; 56:1095–7. [PubMed: 9329452]
31. Mirra SS, Heyman A, McKeel D, Sumi SM, Crain BJ, Brownlee LM, et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part II. Standardization of the neuropathologic assessment of Alzheimer's disease. *Neurology.* 1991; 41:479–86. [PubMed: 2011243]
32. Braak H, Del Tredici K, Rub U, de Vos RA, Jansen Steur EN, Braak E. Staging of brain pathology related to sporadic Parkinson's disease. *NeurobiolAging.* 2003; 24:197–211.
33. Mattis, S. *Dementia Rating Scale: Professional manual.* Odessa, FL: Psychological Assessment Resources; 1988.
34. Galasko D, Kwo-on-Yuen PF, Klauber MR, Thal LJ. Neurological findings in Alzheimer's disease and normal aging. *Arch Neurol.* 1990; 47:625–7. [PubMed: 2346387]
35. Fahn, SER.; UPDRS program members. Unified Parkinsons Disease Rating Scale. In: Fahn, S.; Marsden, CD.; Goldstein, M.; Caine, DB., editors. *Recent developments in Parkinsons disease.* Florham Park, NJ: Macmillan Healthcare Information; p. 1987p. 153–63.
36. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. *Gerontologist.* 1969; 9:179–86. [PubMed: 5349366]
37. Neary D, Snowden JS, Gustafson L, Passant U, Stuss D, Black S, et al. Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. *Neurology.* 1998; 51:1546–54. [PubMed: 9855500]

38. Pfeffer RI, Kurosaki TT, Harrah CH Jr, Chance JM, Filos S. Measurement of functional activities in older adults in the community. *J Gerontol.* 1982; 37:323–9. [PubMed: 7069156]
39. Mallows CL. Some Comments on Cp. *Technometrics.* 1973; 15:661–75.
40. Franssen EH, Kluger A, Torossian CL, Reisberg B. The neurologic syndrome of severe Alzheimer's disease. Relationship to functional decline. *Arch Neurol.* 1993; 50:1029–39. [PubMed: 8215960]
41. Waite LM, Broe GA, Grayson DA, Creasey H. Motor function and disability in the dementias. *Int J Geriatr Psychiatry.* 2000; 15:897–903. [PubMed: 11044871]
42. Bradshaw JM, Saling M, Anderson V, Hopwood M, Brodtmann A. Higher cortical deficits influence attentional processing in dementia with Lewy bodies, relative to patients with dementia of the Alzheimer's type and controls. *J Neurol Neurosurg Psychiatry.* 2006; 77:1129–35. [PubMed: 16772356]
43. Janvin C, Aarsland D, Larsen JP, Hugdahl K. Neuropsychological profile of patients with Parkinson's disease without dementia. *Dement Geriatr Cogn Disord.* 2003; 15:126–31. [PubMed: 12584427]
44. Salmon DP, Galasko D, Hansen LA, Masliah E, Butters N, Thal LJ, et al. Neuropsychological deficits associated with diffuse Lewy body disease. *Brain Cogn.* 1996; 31:148–65. [PubMed: 8811990]
45. Mortimer JA, Ebbitt B, Jun SP, Finch MD. Predictors of cognitive and functional progression in patients with probable Alzheimer's disease. *Neurology.* 1992; 42:1689–96. [PubMed: 1513455]
46. Boyle PA. Assessing and predicting functional impairment in Alzheimer's disease: the emerging role of frontal system dysfunction. *Curr Psychiatry Rep.* 2004; 6:20–4. [PubMed: 14738700]
47. Ballard C, Walker M, O'Brien J, Rowan E, McKeith I. The characterisation and impact of 'fluctuating' cognition in dementia with Lewy bodies and Alzheimer's disease. *Int J Geriatr Psychiatry.* 2001; 16:494–8. [PubMed: 11376465]

Table 1

Demographic and Clinical Characteristics of Dementia with Lewy Bodies (DLB) and Alzheimer's Disease (AD) Patients

	DLB M ± SD (Range)	AD M ± SD (Range)
Age, y	73.9 ± 5.9 (63–87)	73.6 ± 5.1 (63–83)
Education, y	15.0 ± 2.6 (9–20)	14.6 ± 3.0 (9–20)
MMSE (0–30)	21.8 ± 4.5 (10–29)	22.0 ± 4.5 (11–28)
Women : Men	14 : 25	18 : 21
Duration of Illness, y	3.7 ± 2.3 (0–10)	5.1 ± 3.5 (1–15)
Time from Evaluation to Death, y	4.0 ± 2.3 (0–10)	5.3 ± 2.5 (0–14)
Modified Hachinski Score (0–12)	0.4 ± 0.9 (0–5)	0.4 ± 0.7 (0–3)
Braak Stage	3.3 ± 1.9 (0–6)	5.5 ± 0.8 (4–6)*

* Note: Groups differ significantly (Mann-Whitney U = 214.5, $p < 0.001$).

Table 2

	DLB M ± SD (Range)	AD M ± SD (Range)
Cognitive Index (0–144)	107.0 ± 16.7 (60–136)	112.8 ± 14.7 (83–141)
Motor Index (0–20)	4.7 ± 5.3 (0–18)	2.3 ± 3.2 (0–13)
Behavioral Index (0–9)	1.5 ± 1.5 (0–6)	1.5 ± 1.5 (0–6)
Physical ADL (6–30)	8.0 ± 2.3 (6–14)	6.9 ± 1.4 (6–12)
Instrumental ADL (0–20)	13.1 ± 4.4 (3–20)	11.4 ± 4.9 (0–20)

Full Regression Models for Physical Activities of Daily Living (PADL) and Instrumental Activities of Daily Living (IADL) in Dementia with Lewy Bodies (DLB) and Alzheimer's Disease (AD) Patients.

Group	Index	Adjusted R ²	F statistic	p value	Std. Beta	Beta p value
PADL						
DLB	Full Model	0.15	3.3 _(3,35)	<0.05		
	1. Motor				0.35	<0.05
	2. Cognitive				-0.24	0.14
AD	3. Behavioral				-0.10	0.98
	Full Model	0.33	7.1 _(3,35)	<0.001		
	1. Motor				0.33	<0.05
	2. Cognitive				-0.17	0.28
	3. Behavioral				0.36	<0.05
	IADL					
DLB	Full Model	0.39	9.0 _(3,35)	<0.001		
	1. Motor				0.44	<0.01
	2. Cognitive				-0.29	<0.05
AD	3. Behavioral				0.16	0.23
	Full Model	0.44	11.1 _(3,35)	<0.001		
	1. Motor				0.04	0.76
	2. Cognitive				-0.44	<0.01
	3. Behavioral				0.38	<0.01

Technical Appendix Table 4

Best Fit Regression Models for Physical Activities of Daily Living (PADL) and Instrumental Activities of Daily Living (IADL) in Dementia with Lewy Bodies (DLB) and Alzheimer’s Disease (AD) Patients.

Group	Predictor Entry	R ² Change	F Change	R ² Change	p value	Std. beta Step 1	Std. beta Step 2
PADL							
DLB	1. Motor	0.17	7.5 _(1.37)	<0.01	0.41	--	--
AD	1. Behavioral	0.23	11.0 _(1.37)	<0.01	-0.48	0.41	0.41
	2. Motor	0.13	7.3 _(1.36)	<0.05	--	0.37	0.37
IADL							
DLB	1. Motor	0.32	17.1 _(1.37)	<0.001	0.56	0.48	0.48
	2. Cognitive	0.10	5.9 _(1.36)	<0.05	--	-0.32	-0.32
AD	1. Cognitive	0.36	20.9 _(1.37)	<0.001	-0.60	-0.45	-0.45
	2. Behavioral	0.13	8.8 _(1.36)	<0.01	--	0.38	0.38