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RESEARCH ARTICLE

Effects of white matter hyperintensities, neuropsychiatric symptoms, and cognition on activities of daily living: Differences between Alzheimer's disease and dementia with Lewy bodies

Saira Saeed Mirza[1,2] | **Usman Saeed**[3] | **Joel Ramirez**[2,3,4] | **Nathan Herrmann**[2,5] | **Donald T. Stuss**[6,†] | **Sandra E. Black**[1,2,3,4] | **Mario Masellis**[1,2,3]

[1]Division of Neurology, Department of Medicine, University of Toronto, Toronto, Ontario, Canada

[2]Hurvitz Brain Sciences Research Program, Sunnybrook Research Institute, University of Toronto, Toronto, Ontario, Canada

[3]LC Campbell Cognitive Neurology Research Unit, Sunnybrook Research Institute, University of Toronto, Toronto, Ontario, Canada

[4]Heart and Stroke Foundation Canadian Partnership for Stroke Recovery, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Ontario, Canada

[5]Department of Psychiatry, Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada

[6]Department of Psychology, Faculty of Arts and Science, Department of Medicine (Neurology), Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada

Correspondence
Saira Saeed Mirza, Research Associate, Division of Neurology, Department of Medicine, University of Toronto, Hurvitz Brain Sciences Research Program, Sunnybrook Research Institute, Sunnybrook Health Sciences Centre, 2075 Bayview Ave. Room M6-194, Toronto, ON M4N 3M5, Canada.
Email: saira.mirza@sunnybrook.ca; saira.mirza@mail.utoronto.ca

[†]Late Prof. Donald T. Stuss (1941–2019).

Abstract

Introduction: Disability is common across Alzheimer's disease (AD) and dementia with Lewy bodies (DLB). White matter hyperintensities (WMHs) are prevalent in both diagnoses and associated with disability; both diagnoses show neuropsychiatric symptoms (NPS) and impaired cognition.

Methods: In AD and DLB, we examined if WMHs, NPS, and cognition associate with basic and/or instrumental activities of daily living (BADLs and/or IADLs) cross-sectionally, and longitudinally over ≈1.4 years.

Results: Across both diagnoses, NPS were not only associated with greater disability in performing both BADLs and IADLs, but were also associated with a decline in the ability to perform BADLs in the AD group. In the DLB group only, higher WMH volume was associated with greater disability in performing both BADLs and IADLs, and was associated with a decline in the ability to perform BADL over time.

Discussion: Management of NPS and WMHs, particularly in DLB, might help maintain functionality in dementia patients for longer.

KEYWORDS
activities of daily living, Alzheimer's disease and dementia with Lewy bodies, neuropsychiatric symptoms, white matter hyperintensities

1 | INTRODUCTION

Disability in performing activities of daily living (ADLs) is a common feature of all dementias, including Alzheimer's disease (AD) and dementia with Lewy bodies (DLB)—the two most common forms of neurodegenerative dementia. This functional disability creates a huge social, economic, and caregiver burden in addition to increasing patient suffering.

Sociodemographic factors, degree of cognitive impairment, behavioral status, cerebrovascular pathology, and other co-morbidities might influence the ability to perform basic and instrumental activities in people with dementia[1–3]; however, the relative contribution of these determinants possibly differs according to the underlying dementia diagnosis/pathology.

Persons with DLB have more disability than persons with AD of comparable cognitive status, which may be attributed to the motor and behavioral deficits in DLB, which occur early in the course of the disease.[4] Specifically, the contribution of cognitive, motor, and behavioral deficits toward disability differs between AD and DLB.[4] In DLB, self-care activities may be more affected than in AD, whereas in AD, instrumental activities are first and more prominently affected.[5] During the course of AD, basic activities are relatively preserved when compared to instrumental ones.[6] A study comparing change in general cognition, neurological signs, memory test performance, psychiatric symptoms, and functionality in patients with probable DLB and probable AD showed that over time, neurological and functional changes were similar in the DLB and AD groups.[7]

A recent study suggested that neuropsychiatric symptoms (NPS) including apathy, aberrant motor behavior, and appetite disturbance associate with decline in both basic and instrumental activities over 5 years[8] in people with AD; however, another study found that aberrant motor behavior was not associated with basic activities of daily living (BADLs) or instrumental activities of daily living (IADLs), and that global cognition predicts decline in performance of instrumental activities in people with AD.[9] Because NPS are prevalent in DLB as well,[7,10] these associations might be relevant for functionality in people with DLB; however, this remains unexplored.

White matter hyperintensities (WMHs), indicating cerebral small vessel disease in most cases, are highly prevalent in both AD and DLB.[11,12] Like cognitive impairment and NPS, they are associated with disability, likely through the additional cognitive, behavioral, and motor deficits that they cause in conjunction with the neurodegenerative pathology. In non-disabled elderly persons, WMHs are associated with a reduced level of functionality.[13] In dementia, the association of WMHs and disability is even more important, as it may determine the trajectory of independent functioning. In newly diagnosed persons with AD, severe deep WMHs, evaluated according to the modified criteria of Fazekas[14] and Sheltens,[15] were associated with worse performance on BADLs but not IADLs.[16] Another study using a locally developed visual rating scale reported that severe total WMHs were associated with disability in IADLs but not BADLs in persons with amnestic mild cognitive impairment (aMCI).[17] Frontal WMH volume quantified by an automatic segmentation program in women (65–85 years) with aMCI and AD were associated with disability in IADLs; however, associations with BADLs were not tested.[18] The Leukoaraiosis And DISability study (LADIS), which aims to investigate if age-related white matter changes affect functionality in non-disabled elderly, reported that severe WMH burden is associated with a steeper decline in IADL performance over 1 to 3 years; associations with BADLs were not tested.[19,20] Thus the association between WMHs and disability in AD remains debated; most studies have utilized visual grading scales for WMHs,[16–18] longitudinal studies are scarce, and more importantly, this association remains unexplored in DLB. In addition, very few studies for AD have tested associations with both BADLs and IADLs. Because WMHs are prevalent in both diagnoses, having a better understanding of their impact on BADLs and IADLs in each patient group is imperative.

Therefore, in this study, we aimed to investigate if WMH volume (quantitatively measured), NPS, and cognitive functions associate with and/or predict disability in BADLs and/or IADLs in AD and DLB. Although these associations have been tested separately in previous studies, we attempted to fill in the knowledge gaps with an integrated model that includes WMH volume, NPS, and cognitive functions to predict BADLs and IADLs in two of the most common neurodegenerative dementias, that is, AD and DLB.

RESEARCH IN CONTEXT

1. **Systematic Review**: Authors reviewed literature using PubMed. Disability is a common feature across Alzheimer's disease (AD) and dementia with Lewy bodies (DLB)—the two most common neurodegenerative dementias. Both have prevalent white matter hyperintensities (WMHs), neuropsychiatric symptoms (NPS), and cognitive impairment; however, it remains unexplored how these determinants predict disability in dementia patients, particularly in DLB.
2. **Interpretation**: Higher NPS were associated with increasing disability in the AD group over time, whereas higher WMH volume predicted increasing disability over time in DLB patients in particular. These results emphasize that associations of WMHs and disability may also be highly relevant for dementia diagnoses other than AD.
3. **Future Directions**: Management of NPS and preventative strategies for WMHs, such as treatment and strict monitoring of cardiovascular risk factors, may result in preservation of functionality for longer in patients with dementia. Studies with larger sample sizes and longer follow-up are needed.

2 | METHODS

2.1 | Setting

This work was embedded within the Sunnybrook Dementia Study (SDS) (ClinicalTrials.gov: NCT01800214)—a prospective observational

study of dementia patients.[21] The SDS is approved by the local research ethics board at Sunnybrook Health Sciences Centre and written informed consent was obtained from all participants and/or their surrogate caregivers according to the Declaration of Helsinki.

2.2 | Study population

We included 246 persons with dementia (202 with AD and 44 with DLB) with varying degrees of cerebral small vessel disease, who underwent standardized volumetric magnetic resonance imaging (MRI), a comprehensive cognitive test battery, and assessment of NPS and ADLs within 3 months. This constituted the cross-sectional sample for our study. ADLs were reassessed after an average of 1.4 years (0.7–5.5 years) in 127 persons with AD and in 25 with DLB, which constituted the sample for our longitudinal analysis. In AD and DLB cases, acute and subacute strokes were excluded based on review of Diffusion-weighted images/Apparent diffusion coefficient (DWI/ADC) scans. We also excluded all persons with cortical strokes and medium- to large-vessel territory strokes as documented on MRI. Persons with any history of a clinical stroke were also excluded. A qualified research neuroradiologist (Board certified neuroradiologist, China; two research fellowships in Radiology, Canada) with 22 years of experience (reading and rating >5000 scans) in the field reviewed all MR images to ensure theses exclusion criteria were applied uniformly across the SDS cohort.

2.3 | Diagnosis of dementia

AD was diagnosed on recruitment, using the Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria,[22] whereas DLB was diagnosed using the Third Report of DLB Consortium criteria.[23] Diagnoses were confirmed on clinical follow-up. Diagnostic consensus was achieved through review by at least two physicians (MM, NH, and SEB) with expertise in dementia diagnosis.

2.4 | MRI (quantification of white matter hyperintensities)

MRI scans were acquired on a 1.5-Tesla Signa system (GE Healthcare, Milwaukee, WI). Three sets of structural MRI sequences were used: T1-weighted, T2-weighted, and proton density (PD)–weighted. Details are provided in the Supplement and elsewhere.[24]

MRI studies were processed using the Semi-Automated Brain Region Extraction and Lesion Explorer processing pipeline,[25] with excellent interclass correlation and high inter-rater reliability.[26,27] WMHs were identified as lesions that appear as punctate or diffuse regions of hyperintense signal on T2/PD MRI. These images were used to quantify total, deep, and periventricular WMH volumes in mm^3, which were adjusted for total intracranial volume (TIV) as follows: TIV adjusted WMH volumes = $[(\text{raw WMH volume}/\text{TIV}) \times 10^6]$.[24]

2.5 | Activities of daily living

ADLs were assessed using the Disability Assessment in Dementia (DAD) Scale,[28] which measures disability in community-dwelling persons with dementia during the preceding 2 weeks. DAD is administered to a caregiver and takes 15 to 20 minutes to complete. It consists of 40 items regarding BADLs and IADLs: for example, "During the past two weeks, did Mr/Ms. X, without help or reminder, undertake to wash himself/herself or to take a bath or a shower?" Each item can be scored as 1 = yes, 0 = no, or not applicable (NA). The items rated as NA are not included in the total score.[28]

BADLs include activities important for self-care, that is, dressing, maintaining hygiene and continence, eating, and ambulating. IADLs include relatively more complex activities that are important for maintenance in a specific environment such as communication, transportation, shopping, meal preparation, maintaining a household, managing finances, taking medication, staying safe at home, and leisure or recreational activities, which are evaluated in terms of interest shown toward these activities.

For each BADL and IADL, we obtained a total score by adding the score for each question and converted this to a percentage. For both scores, higher score corresponds to less disability.

2.6 | Neuropsychological test battery and cognitive factor scores

Participants underwent a neuropsychological battery (13 tests) performed within 90 days of MRI acquisition. Trained psychometrists blinded to neuroimaging and dementia diagnosis administered all tests; details of the neuropsychological test battery are provided elsewhere.[29] We used Confirmatory Factor Analysis (CFA) to reduce data and calculate the following cognitive factor scores that were used in analysis: attention/executive functions, learning and memory, and language. We included Benton Line Orientation as a measure of visuospatial function, because factor score for visuospatial function could not be calculated. Details of test battery and score calculation are presented in the Supplement file. The number of patients who completed each cognitive test differed; this variability in completion was dependent on dementia severity.

2.7 | Neuropsychiatric symptoms

NPS were assessed using the Neuropsychiatric Inventory (NPI) questionnaire, which includes the following items: delusions, hallucinations, agitation or aggression, depression, anxiety, euphoria, apathy, disinhibition, irritability, aberrant motor behavior, nighttime behavior, and appetite.[30]

2.8 | Covariates

Age, sex, education (recorded as formal years of education), diabetes mellitus type 2 and hypertension (yes/no-validated by medical

records), and clinical dementia diagnosis were considered important covariates and recorded at baseline. Global cognition was assessed by the Mini-Mental Status Examination (MMSE)[31]; however, MMSE score was only used to compare cognition in AD and DLB at baseline. For analyses, we used domain specific cognitive factor scores. Dementia diagnosis was categorized as AD or DLB. We also calculated time between the two ADL assessments for each participant to use as a covariate in the longitudinal analyses.

2.9 | Statistical analyses

TIV-adjusted WMH volumes were log-transformed to achieve a normal distribution and standardized by calculating z-scores to facilitate interpretation.

To reduce the neuropsychological data, we constructed comprehensive factor scores (latent constructs) for attention/executive functions, learning and memory, and language for each participant by using CFA, and used them as predictors in our analyses. CFA uses all available information for any model specified instead of a complete case analysis, and obtained factors are allowed to correlate. Adequacy of model fit to the data was assessed by Comparative Fit Index (CFI- range: 0–1; recommended $\geq$ 0.95), Root Mean Square Error of Approximation (RMSEA range 0–1; recommended $\leq$0.06), and the Standardized Root Mean Square Residual (SRMR range 0–1; recommended $\leq$0.08). The factor score for visuospatial function could not be calculated because the model did not converge statistically. We therefore used Benton Line Orientation test in our analyses as a measure of visuospatial function.

Baseline characteristics were compared between AD and DLB groups using *t*-tests for continuous and chi-square test for categorical variables. We also made item-wise comparisons of the NPI score between AD and DLB using the Wilcoxon rank-sum test.

Using multiple linear regression with backward stepwise selection, we tested cross-sectional and longitudinal associations of WMH, NPI score, and cognitive domains, that is, attention/executive functions, learning and memory, and language, with BADLs and IADLs in the total sample (cross-sectional $n = 246$; longitudinal $n = 152$). Subsequently, associations were tested in AD (cross-sectional $n = 202$; longitudinal $n = 129$) and DLB (cross-sectional $n = 44$; longitudinal $n = 25$), separately. For longitudinal analyses, we used ADL scores at follow-up as outcome, adjusting for baseline ADL scores.

Backward stepwise selection was preferred given the small sample size, particularly for the stratified analyses so that only the significant predictors are retained. For all analyses, a significance cutoff of 0.05 was used. We also tested interaction terms of clinical diagnosis with WMH (Clinical diagnosis × WMH) and with NPI (Clinical diagnosis × NPI) in the full samples.

For all analyses, that is, cross-sectional and longitudinal models with BADLs and IADLs for full and stratified samples, analyses started with all predictors in the model, that is, WMH, NPI score, factor scores for attention/executive functions, learning and memory, language, Benton Line Orientation for visuospatial function, age, sex, years of education, dementia diagnosis (full sample only), hypertension, and diabetes mellitus type 2. Longitudinal models additionally included time between two ADL assessments and respective baseline ADL scores.

Secondary analyses including hippocampal volume as a predictor were performed in a subset of sample where hippocampal volumes were available, in both cross-sectional (AD = 114; DLB = 30) and longitudinal models (AD = 71; DLB = 18).

All analyses were performed using the Stata Software Version 14.1 (StataCorp, College Station, TX, USA).

3 | RESULTS

In the CFA, single confirmatory factor models for all three cognitive factors tested showed excellent fit to the data: attention/executive (CFI = 0.98, RMSEA = 0.04, SRMR = 0.03); learning and memory (CFI = 0.99, RMSEA = 0.04, SRMR = 0.009); and language (CFI = 1.00, RMSEA = <0.0001, SRMR = <0.0001).

Baseline characteristics of the total study population and by AD and DLB groups are summarized in Table 1. Compared to AD, patients with DLB were younger ($P < .001$), had higher MMSE score ($P < .001$) and lower WMH volume ($P < .001$), but more NPS ($P < .001$) and disability in ADLs ($P < .001$) at baseline. Among NPS, hallucinations, agitation, euphoria, apathy, disinhibition, irritability, motor aberration, and nighttime and appetite disturbance were significantly higher in patients with DLB. Depressive symptoms were higher in patients with AD (Table 2). Patients who were lost to follow-up were older ($P = .008$) and had a lower MMSE ($P < .001$) at baseline than those who were included in the longitudinal analysis.

3.1 | Alzheimer's disease and dementia with Lewy bodies combined

Cross-sectional analysis included 246 dementia patients (AD, $n = 202$; DLB, $n = 44$). In this sample, higher WMH volume, NPI score, and years of education were associated with greater disability in BADLs. Years of education by age groups (group 1, $n = 44$): <=60 years; group 2, $n = 159$: >60 to 80 years; group 3, $n = 43$: >80 years) showed that people older than 80 years of age had a lower mean compared to the younger groups; however, the difference was not statistically significant (data available on request).

Higher NPI score and age were associated with greater disability on IADLs, whereas higher attention/executive functions and memory scores were associated with better performance of IADLs (Table 3). We observed a significant interaction between WMHs and clinical diagnosis for BADLs ($P = .001$), but not for IADLs ($P = .114$).

Longitudinal analysis included 152 patients (AD, $n = 127$; DLB, $n = 25$). Higher NPI score and diagnosis of DLB were associated with a decline in the ability to perform BADLs (*p-interaction WMH × Diagnosis = 0.150*), whereas higher learning and memory, visuospatial function, and BADL scores at baseline predicted maintenance of BADL at follow-up (Table 4). Similarly, higher learning and memory, visuospatial function, and IADL scores at baseline predicted maintenance of IADL

TABLE 1 Baseline characteristics of the study population

	Descriptives			
	Total sample	Alzheimer's disease	Dementia with Lewy bodies	
Characteristics	*N* = 246	*n* = 202	*n* = 44	*P*-value
Age	70.7 (10.0)	72.1 (9.5)	64.6 (10.1)	<**.001**
Women, *n* (%)	127 (51.6)	111 (54.9)	16 (36.4)	.11
Education, years	14.1 (3.9)	14 (3.9)	14.8 (4.0)	**.001**
MMSE score	24.1 (3.7)	23.8 (3.5)	25.1 (4.2)	<**.001**
NPI score	12.5 (14.4)	10.6 (13)	21.3 (17.1)	<**.001**
TIV-adjusted WMH volume, cm^3	6.2 (9.1)	6.9 (9.7)	3.0 (3.9)	<**0.001**
Deep	0.77 (1.0)	0.8 (1.0)	0.5 (0.8)	<**.001**
Periventricular	5.4 (8.6)	6.0 (9.3)	2.5 (3.4)	<**.001**
TIV-adjusted hippocampal volume, cm^3[a]	4.4 (0.6)	4.4 (0.6)	4.4 (0.6)	.94
HTN present, *n* (%)	85 (34.6)	71 (35.1)	14 (31.8)	.19
Diabetes present, *n* (%)	23 (9.3)	21 (10.4)	2 (4.5)	**.001**
BADL score	94.0 (10.0)	94.5(9.7	91.5 (11.1)	<**.001**
IADL score	72.3 (24.2)	73.6 (24.5)	66.5 (22.0)	**.0001**

TIV, total intracranial volume; WMH, white matter hyperintensities; ADL, activities of daily living; BADL, basic activities of daily living; IADL, instrumental activities of daily living.
Values are means (standard deviation) or counts (percentage).
P-values are based on *t*-tests (performed with log-transformed values for WMH) for continuous and chi-square tests for categorical variables.
WMHs and hippocampal volumes were adjusted for TIV as follows: TIV adjusted volumes = [(raw WMH or hippocampal volume/TIV) × 10^6].
Mean ADL scores at follow-up in full sample (*n* = 152): BADL: 86.2 ± 19.9; IADL: 57.4 ± 30.6.
[a]Hippocampal volumes were available for a subset of sample. (*N* = 144; AD = 114; DLB = 30).

TABLE 2 Neuropsychiatric symptoms in AD and DLB

Neuropsychiatric symptoms (NPI)	Alzheimer's disease, *n* = 202	Dementia with Lewy bodies, *n* = 44	*P*-value
Delusions	0.5 (1.4)	0.5 (2.0)	.25
Hallucinations	013 (0.8)	0.3 (1.3)	**.001**
Agitation	1.0 (2.1)	1.7 (2.6)	<**.001**
Depression	1.2 (1.9)	1.1 (2.3)	**.009**
Anxiety	1.2 (2.4)	1.6 (3.1)	.18
Euphoria	0.2 (1.1)	1.2(2.4)	<**.001**
Apathy	1.9 (2.8)	4.5 (3.8)	<**.001**
Disinhibition	0.5 (1.5)	1.7 (3.5)	<**.001**
Irritability	1.4 (2.5)	2.0 (3.3)	**.009**
Aberrant motor behavior	0.8 (2.3)	2.0 (3.5)	<**.001**
Nighttime disturbance	0.9 (1.8)	1.8 (3.2)	**.001**
Appetite disturbance	1.0 (2.3)	2.6 (3.5)	<**.001**

Values are means (standard deviation).
P-values are based on Wilcoxon rank-sum test

at follow-up (Table 4). We did not find significant interaction between clinical diagnosis and NPI score in any of the analyses.

Subsequently, we stratified analyses based on diagnosis. This stratification was based on an a priori assumption that associations might differ between AD and DLB.

3.2 | Alzheimer's disease

Cross-sectionally, higher NPI score was associated with disability in both BADLs and IADLs. Female sex was associated with better performance on BADLs, whereas better attention/executive functions and

TABLE 3 Variables associated with the ability to perform activities of daily living in the combined and stratified sample: cross-sectional analyses

Cross-sectional analysis, (β, 95% CI)						
	Basic activities of daily living			*Instrumental activities of daily living*		
	Predictors	**Difference (95% CI)**	***P*-value**	**Predictors**	**Difference (95% CI)**	***P*-value**
Full sample, N = 246						
	zlogWMH	-1.71 (-2.98, -0.41)	.010	NPI	-0.87 (-1.05, -0.69)	<.001
	NPI	-0.28 (-0.37, -0.19)	<.001	Age	-0.37 (-0.64, -0.10)	.007
	Years of education	-0.44 (-0.77, -0.11)	.008	Memory	0.43 (0.06, 0.79)	.022
				Executive functions	4.69 (2.35, 7.03)	<.001
Alzheimer's disease, n = 202						
	NPI	-0.29 (-0.39, -0.20)	<.001	NPI	-0.91 (-1.14, -0.68)	<.001
	Years of education	-0.32 (-0.64, -0.004)	.047	Memory	0.48 (0.02, 0.94)	.042
	Women	2.97 (0.51, 5.44)	.018	Executive functions	3.91 (1.28, 6.54)	.004
Dementia with Lewy bodies, n = 44						
	zlogWMH	-7.50 (-11.68, -3.32)	.001	zlogWMH	-7.48 (-13.3, -1.66)	.013
	NPI	-0.28 (-0.51, -0.04)	.021	NPI	-0.72 (-1.04, -0.40)	<.001
	Executive functions	5.43 (1.73, 9.14)	.005	Executive functions	8.08 (2.98, 13.18)	.003

Coefficients are derived from multiple linear regression with backward stepwise selection
Variables included in the model: zlogWMH (white matter hyperintensities) volume, NPI (neropsychaitric inventory) score, factor scores for attention/executive functions, learning and memory, language, and Benton Line Orientation score, age, sex, years of education, diabetes mellitus type 2, hypertension, and clinical diagnosis-AD/DLB (full sample only).

learning and memory were associated with better performance on IADLs (Table 3).

Longitudinally, higher NPI score at baseline was associated with significant decline in the ability to perform BADLs in this group (Table 4), whereas higher learning and memory, visuospatial function, and BADL scores at baseline predicted maintenance of BADLs at follow-up. For IADLs, visuospatial function and IADL scores at baseline were significant predictors (Table 4).

3.3 | Dementia with Lewy bodies

Cross-sectionally, higher WMH volume and NPI score were associated with greater disability in performing both BADLs and IADLs (Table 3). Higher attention/executive functions score was associated with better performance on both BADLs and IADLs (Table 3).

Longitudinally, higher WMH volume at baseline predicted significant decline in the ability to perform BADLs at follow-up. Higher executive functions score predicted maintenance of BADLs, whereas higher learning and memory score at baseline predicted better performance of both BADLs and IADLs (Table 4).

Hippocampal volume was not a significant predictor in any cross-sectional analysis. In longitudinal analyses, greater hippocampal volume was associated with better functionality in performing BADLs in AD (β: 5.9; 95% confidence interval [CI]: 0.09, 10.1) in AD, and in both BADLs (β: 32.6; 95% CI: 13.0, 52.2) and IADLs (β: 23.8; 95% CI: 9.1, 38.5) in DLB.

4 | DISCUSSION

The key findings of this study are that (1) higher NPS were not only associated with greater disability in performing both basic and instrumental activities in AD and DLB, but were also associated with a decline in the ability to perform basic activities in the AD group; and (2) higher WMH volume was associated with greater disability in performing both basic and instrumental activities in the DLB group only, and was also associated with a decline in the ability to perform basic activities in DLB over 1.4 years. Remarkably, we did not observe any associations of WMH volume and disability in the AD group, despite the significantly higher WMH burden in AD than DLB group and larger sample size. These results emphasize that associations of WMH and disability may also be highly relevant for dementia diagnoses other than AD.

In AD and DLB combined, higher education was associated with greater disability in basic activities. Studies have shown that although highly educated people are more resilient to cognitive impairment, once impairment starts, they tend to decline faster compared to their less-educated counterparts,[32] and this might explain our finding. In both diagnoses, better executive functions associated with lesser disability and higher baseline memory predicted maintenance of BADLs.

TABLE 4 Variables associated with decline in the ability to perform activities of daily living in the combined and stratified sample: longitudinal analyses

Predictors of functionality over 1.4 years (β, 95% CI)						
	Basic activities of daily living			*Instrumental activities of daily living*		
	Predictors	**Decline (95% CI)**	***P*-value**	**Predictors**	**Decline (95% CI)**	***P*-value**
Full sample, N = 152						
	NPI	-0.34 (-0.54, -0.15)	<.001	NPI	-0.33 (-0.63, -0.04)	.03
	Memory	0.59 (0239, 0.96)	.002	Memory	1.19 (0.64, 1.75)	<.001
	BADL at baseline	0.75 (0.42, 1.08)	<.001	IADL at baseline	1.15 (0.65, 1.65)	<.001
	Benton line orientation	0.38 (0.08, 0.69)	.014	Benton line orientation	1.03 (0.65, 1.65)	<.001
	Diagnosis (DLB)	-0.76 (-15.07, -0.05)	.048			
Alzheimer's disease, n = 127						
	NPI	-0.35 (-0.56, -0.15)	.001	IADL at baseline	0.85 (0.69, 1.02)	<.001
	Memory	0.44 (0.03, 0.85)	.034			
	BADL at baseline	0.71 (0.38, 1.04)	<.001	Benton line orientation	0.79 (0.36, 1.23)	<.001
	Benton line orientation	0.36 (0.06, 0.66)	.017			
Dementia with Lewy bodies, n = 25						
	zlogWMH	-11.09 (-21.90, -0.28)	.045	Memory	0.77 (0.33, 1.21)	.002
	Age	1.05 (0.03, 2.07)	.045	IADL at baseline	1.25 (0.31, 2.19)	.011
	Memory	10.7 (2.20, 19.21)	.016			
	Executive functions	14.8 (6.01, 23.65)	.002			

Coefficients are derived from multiple linear regression with backward stepwise selection, using ADL scores at follow-up as outcome.
Variables included in the model: zlogWMH (white matter hyperintensities) volume, NPI (neuropsychaitric inventory) score, factor scores for attention/executive functions, learning and memory, language, Benton Line Orientation score, age, sex, years of education, diabetes mellitus type 2, hypertension, clinical diagnosis-AD/DLB (full sample only), respective ADL scores at baseline, and time between two ADL assessments.

Better visuospatial function at baseline predicted maintenance of functionality in the AD group.

NPS including apathy, agitation, and aberrant motor behavior, disinhibition, and nighttime and appetite disturbances were more prevalent in DLB than in AD in our sample, as shown by others.[7,33,34] Depression was more prevalent in the AD group; however, higher total NPI score was associated with greater disability across both diagnoses. We did not test item-wise associations of NPI with ADLs due to limited sample, and because our aim was to account for total NPI score as a determinant of disability. Previously, a high prevalence (69%) of NPS has been reported in AD, and that depression, apathy, agitation, anxiety, aberrant motor behavior, irritability, sleep disturbance, and eating disorders were all associated with greater disability in performing IADLs.[35] In a 5-year follow-up study of AD, apathy, aberrant motor behavior, and appetite disturbances were related to a decline in the ability to perform both basic and instrumental activities[8]; there are no longitudinal studies for DLB. Because neuropsychiatric symptoms may appear early in the course of dementia, such as in MCI,[36] addressing them may lead to maintenance of functionality for relatively longer periods and reduced caregiver burden.

Cross-sectionally, associations of WMHs with both BADLs and IADLs were found only in the DLB group despite greater WMH burden in the AD group. This might be partly because of prevalent parkinsonism in DLB. It is possible that motor deficits in the form of parkinsonism might be aggravated by the co-occurrence of WMHs in DLB patients affecting the execution of a task. However, unfortunately, we could not test this hypothesis because parkinsonism was not formally assessed using rating instruments, such as the Unified Parkinson Disease Rating Scale (UPDRS). The LADIS study examined the association between WMHs and ADLs in 639 non-disabled individuals with mild cognitive or motor impairment, minor cerebrovascular events, or mood alterations or those with WMH as an incidental finding. It showed that the WMH severity[14] was related to disability in performing instrumental activities, possibly due to deteriorating executive and motor functions; however, basic activities were not tested.[13] Longitudinally, we found that WMH were related to decline in performing basic activities but not instrumental in the DLB group. Persons with DLB had a mean MMSE score of ≈25 at baseline, which might explain why we did not find a significant decline in the ability to perform IADL over a short follow-up. The decline in the ability to perform BADLs in the DLB group over time might thus be largely attributed to deteriorating motor functions. However, it is likely that associations of baseline WMH with decline in ability to perform IADLs will become apparent in the DLB group as follow-up increases. In addition, disinterest or lack of motivation perhaps

contributes to higher disability in DLB, and that impairment in executive functions might not be the only major determinant of disability in this sample. In a study of Parkinson disease dementia (PDD), a related Lewy body disorder, attentional performance was the most important predictor of ADL cross-sectionally.[37]

The association between WMHs and disability possibly also depends on the stage of the disease, and the underlying mechanisms might also be stage dependent. For instance, our sample includes dementia cases of mild to moderate severity; relevant causes of disability might largely be apathy or motor, rather than executive functional deficits. We speculate that as dementia progresses, the association between WMHs and disability will be explained more by impairment in executive functions, and across other cognitive domains. Thus we might eventually observe associations between WMHs and disability in AD as the disease progresses.

Autonomic failure in DLB can be another biological mechanism underlying the association of WMHs and disability. In α-synucleinopathies, which include DLB, PDD, and Multiple System Atrophy (MSA), autonomic failure of multiple systems has a considerable impact on ADLs.[38] For instance, autonomic urinary dysfunction is the most common dysautonomic feature in α-synucleinopathies.[39] Cardiovascular autonomic dysfunction, manifesting most commonly as orthostatic hypotension, may lead to cerebral hypoperfusion and altered compensatory mechanisms in the brain, thus accelerating degeneration.[40] Orthostatic hypotension, which is the primary feature of cardiovascular autonomic failure in DLB, is associated with postural instability,[41] and is also suggested to increase the risk of WMHs.[42] Reciprocally, studies also suggest that WMHs relate with more neurocardiovascular instability in DLB. In addition, fatigue has been recently recognized as an important non-motor symptom of α-synucleinopathies, which may affect ADLs.[42] PDD patients with pronounced WMHs showed shorter disease duration and a more severe clinical phenotype, suggesting faster neurodegeneration.[43] Functional connectivity studies with resting-state functional MRI (fMRI) have shown distinct network disruptions in DLB, in addition to molecular and structural brain changes,[44] which might result in more or accelerated damage due to the addition of white matter disease. Studies with larger sample sizes and longer follow-up are needed to assess the change in WMH burden over time along with cognitive and functional decline.

Major strengths of our study include testing associations of WMH, NPS, and cognition with disability in an integrated model; use of quantitative WMH volumes, which is more accurate in detecting associations than the semi-quantitative visual grading scales for WMH severity as in most of the above-mentioned studies. We examine all these associations in the two most common neurodegenerative dementias (AD and DLB) cross-sectionally and longitudinally for both BADLs and IADLs, which has not been tested before in an integrated model. Other strengths include a well-characterized cohort of dementia patients, rigorous image-processing methods validated for older adults and mixed dementias, and adjusting for several confounders. There are certain limitations as well. We did not have data evaluating the severity of parkinsonism, and therefore we could not test if associations in DLB were indeed due to motor deficits. The DLB group in the longitudinal analyses had a relatively smaller sample size; thus estimates might not be precise, particularly from the models including hippocampal volume as a predictor. DLB cases might have co-existent AD pathology but this could not be assessed. We also acknowledge that MRI at 3T has improved ability over 1.5T at identifying hyperintense signal changes in the white matter and that this is a potential limitation.

In conclusion, higher NPS were associated with increasing disability in the AD group over time, whereas higher WMH volume predicted increasing disability over time in DLB patients in particular. Management of NPS and preventative strategies for WMHs, such as treatment and strict monitoring of cardiovascular risk factors, may result in preservation of functionality for longer in patients with dementia. This has important implications from the care perspective, as caregivers can help patients with task-oriented planning for activities that might lead to independent execution of tasks by patients in the absence of motor problems.

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CONFLICTS OF INTEREST

Dr. Mirza, Mr. Saeed, Dr. Ramirez, Dr. Herrmann, and Dr. Stuss report no disclosures. Dr. Black reports personal fees for CME from Medscape/Biogen, Eli Lilly, and Novartis; for ad hoc consulting from Novartis, Merck, Eli Lilly, and Pfizer; and contract grants to the institution from GE Healthcare, Eli Lilly, Biogen Idec, Novartis, Genentech, Roche, and Optina. Dr. Masellis reports personal fees for ad hoc consultancy from Arkuda Therapeutics, Ionis Pharmaceuticals, and Alector Pharmaceuticals' royalties from Henry Stewart Talks Ltd.; and grants to the institution from Roche, Novartis, Washington University, and Axovant Sciences.

AUTHOR CONTRIBUTIONS

Saira Saeed Mirza, Donald T. Stuss, Mario Masellis, Nathan Herman, and Sandra E. Black designed the study, Usman Saeed and Joel Ramirez helped in data acquisition, Saira Saeed Mirza and Usman Saeed performed all analyses. Saira Saeed Mirza and Mario Masellis drafted the manuscript. All authors were involved in the interpreted results and critical review of the manuscript.

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