Received: 23 March 2022 | Revised: 23 June 2022 | Accepted: 8 July 2022

DOI: 10.1002/alz.12765

RESEARCH ARTICLE

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

Neuropathological correlates of neuropsychiatric symptoms in dementia

Lucy L. Gibson[1] | Lea T. Grinberg[2,3] | Dominic ffytche[1] | Renata E. P. Leite[3] | Roberta D. Rodriguez[3] | Renata E. L. Ferretti-Rebustini[4] | Carlos A. Pasqualucci[3] | Ricardo Nitrini[3] | Wilson Jacob-Filho[3] | Dag Aarsland[1,5] | Claudia K. Suemoto[3]

[1]Old Age Psychiatry Department, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK

[2]Memory and Aging Center, Department of Neurology and Pathology, University of California San Francisco, San Francisco, California, USA

[3]University of São Paulo Medical School, São Paulo, Brazil

[4]University of São Paulo School of Nursing, São Paulo, Brazil

[5]Centre for Age-Related Disease, Stavanger University Hospital, Stavanger, Norway

Correspondence
Lucy L. Gibson, Old Age Psychiatry Department, Institute of Psychiatry, Psychology and Neuroscience, King's College London, 6th floor, London, SE5 8AF, UK.
E-mail: lucy.1.gibson@kcl.ac.uk

Abstract

Introduction: Neuropsychiatric symptoms (NPS) are common in Lewy body disease (LBD), but their etiology is poorly understood.

Methods: In a population-based *post mortem* study neuropathological data was collected for Lewy body (LB) neuropathology, neurofibrillary tangles (NFT), amyloid beta burden, TDP-43, lacunar infarcts, cerebral amyloid angiopathy (CAA), and hyaline atherosclerosis. *Post mortem* interviews collected systematic information regarding NPS and cognitive status. A total of 1038 cases were included: no pathology (NP; n = 761), Alzheimer's disease (AD; n = 189), LBD (n = 60), and AD+LBD (n = 28).

Results: Hallucinations were associated with higher LB Braak stages, while higher NFT Braak staging was associated with depression, agitation, and greater number of symptoms in the Neuropsychiatric Inventory. Cases with dual AD+LBD pathology had the highest risk of hallucinations, agitation, apathy, and total symptoms but a multiplicative interaction between these pathologies was not significant.

Discussion: LB and AD pathology contribute differentially to NPS likely with an additive process contributing to the increased burden of NPS.

KEYWORDS
Lewy body disease, neuropathology, neuropsychiatric symptoms

1 | INTRODUCTION

Lewy body disease (LBD) is a neurocognitive disorder with prominent motor symptoms; it includes Parkinson's disease dementia (PDD) and dementia with Lewy bodies (DLB). Collectively, this is the second most common neurodegenerative dementia after Alzheimer's disease (AD), characterized by the accumulation of aggregated alpha-synuclein in Lewy bodies (LB) and neurites.[1] PDD and DLB are distinguished clinically by the timing of onset of the cognitive impairment, but such clear distinction is not always possible neuropathologically.[2] Almost all patients with LBD are affected by neuropsychiatric symptoms (NPS) during the disease course, with depression, agitation, apathy, and psychosis being particularly common; however, the neuropathological basis for these symptoms is poorly understood.[3] The profile of NPS differs across dementia subtypes and, while psychosis is most common in clinical studies of LBD,[4] there is also increased misdiagnosis of AD as DLB in the presence of psychotic symptoms.[5]

While the neuropathological correlates of NPS are relatively underexplored in DLB, a number of studies have examined this in AD, both in the early stages of disease[6,7] and where pathological processes are more advanced.[8,9] In AD, increased neurofibrillary

tangles (NFT) and burden of hyperphosphorylated tau has been associated with psychosis, agitation, and depression both in the prodromal and later stages.[6,10] Mixed pathologies may also contribute to NPS, with co-morbid LBD pathology associated with increased anxiety and irritability in AD[11] and advanced small vessel disease (SVD) and cerebral amyloid angiopathy (CAA) associated with psychosis.[12]

Clinicopathological studies have shown that more than half of patients with DLB have co-existent AD pathology with phenotypic consequences including accelerated cognitive decline and shorter survival times.[13–15] While several studies have explored the associations between neuropathological changes and cognitive decline,[16–19] the impact of this dual pathology, and other frequently co-occurring neuropathologies such as TDP-43,[20] on the NPS in LBD is not clear.[11,12] Furthermore, studies in LBD have been mostly restricted to end-stage disease with conflicting results; while several studies have suggested that Braak NFT stage may not contribute to visual hallucinations in LBD,[21,22] a more recent study found an association between AD pathology and visual hallucinations (VH) in Parkinson's disease (PD).[23]

Early in PD, minor hallucinations such as illusions, and passage and presence hallucinations often appear, progressing over time to formed VH and later, hallucinations in other modalities.[24,25] The timing and risk factors for this progression mirrors the Braak progression of LB pathology from brainstem to forebrain suggesting an etiological link.[24] However, while increased LB burden in limbic regions has been linked to earlier VH in LBD,[26] to our knowledge, no study to date has demonstrated a clear association between LB progression from an early stage and increasing severity of hallucinations. Where VH occur in the absence of dementia, as is common in PD, LB pathology is not seen in the cortex suggesting that the neuropathological mechanisms underpinning VH may be separated from dementia-related processes.[27]

Neuropathological studies are often limited to highly selected cohorts with end-stage disease and small sample sizes. Studies with a focus on the neurobiological basis of NPS in prodromal disease are scarce and the relationship between pathology and NPS at this stage is particularly unclear. The Biobank for Aging Studies (BAS) is a unique population-based study that includes cases with a wide range of neuropathological outcomes and clinical stages allowing the impact of low burden NFT, amyloid beta (Aβ), and LB to be assessed.[28] Ehrenberg et al. explored the impact of neuropathology in prodromal disease in this sample but they focused exclusively on AD pathology, excluding all co-morbid neuropathologies including LBD.[6]

We aimed to investigate the neuropathological correlates of NPS independent of the overarching neuropathological diagnosis across a range of neuropathological substrates. We chose five clinically important and common NPS (hallucinations, delusions, depression, apathy, and agitation) as the primary outcomes.[4] We also aimed to explore how NPS compare across neuropathologically defined AD and LBD groups, hypothesizing that the greatest burden of NPS would be seen in patients with concomitant AD and LBD pathology indicating an additive or even synergistic mechanism akin to cognitive impairment.

RESEARCH IN CONTEXT

1. **Systematic Review**: The etiology of neuropsychiatric symptoms in Lewy body disease (LBD) and other dementias is poorly understood. A review of the current literature from PubMed is included citing recent publications investigating the contribution of various neuropathologies to the neuropsychiatric symptoms in LBD and Alzheimer's disease (AD). To date, current studies have largely focused on AD at a relatively advanced stage of disease.
2. **Interpretation**: Our findings gave insight as to how the progression of neuropathology contributed to a number of neuropsychiatric symptoms; higher Lewy body Braak stages were associated with greater risk of hallucinations suggesting the evolution of this symptom may track Braak stage. Cases with dual pathology were noted to have the highest burden of neuropsychiatric symptoms suggesting Lewy body and AD pathology may contribute to neuropsychiatric symptoms in an additive process.
3. **Future Directions**: The article highlights the importance of understanding the neurobiological mechanisms contributing to neuropsychiatric symptoms across dementia subtypes. Future studies should include newer neuropathological classification systems and consider the influence of the location of pathology, while continuing to include cases with a wide range of neuropathological outcomes as it seems likely that this low burden pathology does make some contribution to the overall clinical phenotype.

2 | MATERIALS AND METHODS

2.1 | Patient cohort

We used cases collected between 2004 and 2021 from the BAS of the University of São Paulo, Brazil. In São Paulo, autopsy is mandatory where there is no established cause of death, which includes most patients with a non-traumatic cause of death. Inclusion criteria of the BAS requires participants to be at least 18 years of age at death, availability of next of kin with at least weekly contact with the deceased in the 6 months prior to death, and ability of next of kin to provide clinical information and consent to brain donation. BAS exclusion criteria include brain tissue not suitable for neuropathological analyses (cerebrospinal fluid [CSF] pH < 6.5 or major acute brain lesions) or if the clinical data provided by the informant was not consistent across the various measures detailed below.

Cases were classified by neuropathological diagnosis, and for the purposes of this study, we included all participants who exhibited AD-type pathology (plaques and/or NFTs), LBD, or who were without

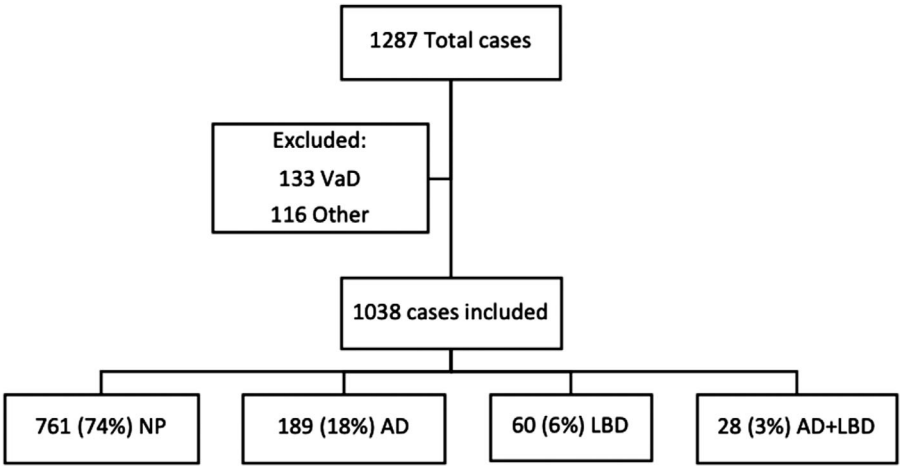

FIGURE 1 Flow diagram of included cases classified by neuropathological diagnosis. AD, Alzheimer's disease; AD+LBD, met criteria for AD and LBD; LBD, Lewy body disease; NP, insufficient neuropathology to meet disease classification; VaD, vascular dementia

sufficient pathology to fulfil a disease diagnosis in neuropathological evaluation. Seven hundred sixty-one (73%) of included participants did not have sufficient neuropathological changes to meet a disease classification (NP), 189 (18%) were diagnosed with AD, 60 (6%) with LBD, and 28 (3%) met the neuropathological criteria for both LBD and AD. Cases with a diagnosis of cerebrovascular pathology (vascular dementia [VaD]; n = 133; one large chronic infarct [>1 cm] or three lacunae [<1 cm]) or an alternative neuropathological diagnosis (n = 116) were excluded in the absence of AD or LB co-pathology (Figure 1). This study was approved by local ethical committees and all informants signed consent forms.

2.2 | Neuropathological assessment

The BAS uses a 14-region immunohistochemistry panel in formalin-fixed paraffin-embedded sections to detect neurodegeneration using universally accepted criteria to stage and diagnose cases.[28,29] Immunohistochemistry was performed in the selected sections with antibodies against Aβ (4G8, 1:10.000; Signet Pathology Systems), phosphorylated tau (PHF-1, 1:2.000; gift from Peter Davies), TDP-43 (1:500, Proteintech), and α-synuclein (EQV-1, 1:10.000; gift from Kenji Ueda).[30–32] After immunostaining for phosphor-Ser396/Ser404 tau, NFT were scored according to Braak stage (0, I/II, III/IV, and V/VI) following conventional categorization.[33,34] Aβ pathology was scored using Consortium to Establish a Registry for Alzheimer's Disease neuropsychological assessment (CERAD-NP) for the density of neuritic plaques (none, sparse, moderate, or frequent).[35] LB neuropathology was classified using the Braak staging 0 through VI for PD.[36] Immunohistochemistry for transactive response DNA-binding protein 43 kDA (TDP-43) was introduced into the protocol in 2012 with a binary classification.[37] Cerebrovascular lesions were assessed by gross macroscopic evaluation of the whole brain and microscopic evaluation of the 14 regions using hematoxylin-eosin stained slides. The presence of lacunar infarcts was registered by topography, stage, size, and number. The diagnosis of SVD included moderate or severe arteriosclerosis/atherosclerosis and lipohyalinosis in three or more cortical regions.[38] CAA was considered present where widespread disease was seen in ≥3 different cortical areas.[38]

2.3 | Neuropathological diagnostic classification

A neuropathological diagnosis of AD was made for individuals with AD Braak stage ≥III and CERAD neuritic plaque density of moderate or frequent. LBD was diagnosed where cases had PD Braak classification ≥III. We used the neuropathological term LBD for all diseases associated with LB, removing the distinction between PD, PDD, and DLB. Neuropathological diagnoses were made blinded to clinical status. In the AD+LBD group subjects had to meet the neuropathological diagnosis for AD and LBD. Those without sufficient neuropathology to meet a disease diagnosis were graded NP (no pathology).

2.4 | Evaluation of symptoms

The deceased's clinical history was obtained from a knowledgeable informant in a semi-structured interview at the time of *post mortem* less than 24 hours after death;[30] this interview has previously been validated for *post mortem* use with high sensitivity and specificity.[39] The clinical interview includes information regarding sociodemographics, medication use, the Neuropsychiatric Inventory (NPI),[40] and cognitive evaluation with the informant section of the Clinical Dementia Rating (CDR), validated in the Brazilian population.[39,41] Cause of death was extracted from the death certificate. Scores from the CDR and 12-item NPI collected in *post mortem* informant interviews reflect the participant's status 3 months before death to avoid the influence of delirium and peri-agonal events.[42] The NPI evaluates 12 domains: agitation, apathy, anxiety, appetite, delusions, depression, disinhibition, elation, hallucinations, irritability, aberrant motor behavior, and sleep. Scores are typically calculated by multiplying frequency$^{1-4}$ and severity$^{1-3}$ for domains with any disturbance. As the median domain scores of

TABLE 1 Sociodemographics and cognitive status according to diagnosis made from neuropathological findings irrespective of clinical status (n = 1038)

	NP (n = 761)	AD (n = 189)	LBD (n = 60)	AD+LBD (n = 28)	*P* value
Age at death (SD)	69.1 (12.6)	81.6 (8.20)	78.4 (8.14)	81.6 (7.91)	<.001***
Female n (%)	335 (44.0)	127 (67.2)	25 (43.2)	20 (67.9)	<.001*
Education in years (SD)	5.31 (4.24)	3.10 (2.96)	3.82 (2.37)	4.86 (4.06)	<.001***
Ethnicity					.025**
White	488 (64.4)	138 (73.0)	45 (75.0)	16 (57.1)	
Black	96 (12.7)	25 (13.2)	2 (3.33)	6 (21.4)	
Mixed	156 (20.6)	24 (12.7)	10 (16.7)	6 (20.7)	
Other	18 (2.37)	2 (1.06)	3 (5.00)	0	
Dementia, n (%)					<.001**
CDR = 0	699 (92.0)	79 (42.0)	37 (61.7)	5 (17.9)	
CDR = 0.5	28 (3.68)	20 (10.6)	7 (11.7)	3 (10.7)	
CDR ≥ 1	33 (4.34)	89 (47.3)	16 (26.7)	20 (71.4)	
Total number symptoms on NPI (SD)	1.43 (1.86)	2.84 (2.56)	2.05 (2.15)	3.54 (2.45)	<.001***

Abbreviations: AD, Alzheimer's disease; AD+LBD, meets classification for AD and LBD; CDR, Clinical Dementia Rating; LBD, Lewy body disease; NP, no neuropathological diagnosis; NPI, Neuropsychiatric Inventory; SD, standard deviation.
*Chi square test used to determine *P* value.
**Fisher's exact test used where cells ≤5 participants.
***One way analysis of variance or Kruskal–Wallis distribution dependent used to determine *P* value.

our participants are zero, this was set as the cut-off for a negative diagnosis, with any score above zero receiving a positive diagnosis.

2.5 | Statistics

One-way analysis of variance and chi-squared tests were used to compare demographic and clinical metrics across groups. For the analysis of cases across neuropathological diagnosis, four neuropathologically defined groups were included NP, LBD, AD, and AD+LBD. Hallucinations, delusions, depression, agitation, and apathy were selected as the primary outcomes due to their clinical relevance in LBD but secondary analysis of the remaining NPS is included in supporting information. Multivariable ordinal logistic regression models assessed the odds of having each NPS for the given pathologic groups (AD, LBD, AD+LBD) compared to reference group (NP). Models were adjusted for age, sex, ethnicity, years of education, cause of death, and use of antidepressant and antipsychotic medication. Cause of death was divided into categories for respiratory, cardiovascular, cancer, and other. For total number of symptoms on the NPI across neuropathological diagnoses, a Poisson multiple linear regression was performed. Secondary analysis with CDR as an additional covariate was also performed.

We also examined the relationships between neuropathological substrates and NPS outside diagnosis; across all cases with diagnostic categories collapsed. Thus, cases with mild but potentially clinically relevant neuropathology, such as lower staging for NFT, Aβ, and LB, were included in the analysis. Multivariable logistic regression was performed with presence of NPS as the binary dependent variable and the neuropathological substrates: LBD staging, NFT staging, CERAD neuritic plaque, lacunar infarcts, CAA, hyaline atherosclerosis, and TDP-43 as the independent variables. LBD, NFT, and CERAD staging were treated as continuous variables to investigate whether the odds of NPS increased in progressing stages. These models were adjusted for age, sex, ethnicity, years of education, cause of death, use of antidepressant and antipsychotic medication, and CDR score. TDP-43 was analyzed separately due to the reduced number of subjects (n = 578). We explored the multiplicative interaction effects between LBD and both NFT and CERAD Aβ. Poisson multiple linear regression was performed for total number of symptoms on the NPI and neuropathological substrates, similarly adjusted.

3 | RESULTS

3.1 | Demographic information

A total of 1038 cases were included of mean age 72.2 (standard deviation [SD] = 12.7), 48.8% of the participants were female and the mean educational level was 4.8 years (SD = 4.03), broadly representative of death data from São Paulo.[28] Regarding ethnicity, 66% of cases were identified by their next of kin as White, 12% as Black, 19% as mixed, and 2% as other. This demographic composition is overall similar to the São Paulo 2010 census but the mixed population was underrepresented (26.5%) and Black population (5.5%) overrepresented. Demographic data stratified by neuropathological diagnosis is shown in Table 1. Cardiovascular causes of death were most common (45.6%), followed by respiratory causes (42.9%). Cancer was listed as a cause of death for 1.6% (n = 17). There was

TABLE 2 Selected neuropsychiatric symptoms stratified by neuropathological diagnostic classification (n = 1031)

	NP (n = 757)	AD (n = 186)	LBD (n = 60)	AD+LBD (n = 28)	*P*
Hallucinations, n (%)	41 (4.2)	38 (20.4)	12 (20)	14 (50)	<.001
NPI mean score (SD)	0.26 (1.44)	1.26 (3.05)	0.97 (2.41)	2.54 (3.37)	
Delusions n, (%)	30 (4)	34 (18.3)	6 (10.2)	5 (17.9)	<.001*
NPI mean score (SD)	0.22 (1.36)	1.16 (2.93)	0.59 (2.21)	0.96 (2.40)	
Depression n, (%)	153 (20.3)	66 (35.5)	21 (35)	10 (35.7)	<.001
NPI mean score (SD)	1.20 (2.89)	1.96 (3.30)	1.92 (2.94)	1.65 (3.22)	
Agitation n, (%)	98 (13.0)	51 (27.3)	7 (11.7)	8 (28.6)	<.001
NPI mean score (SD)	0.69 (2.16)	1.82 (3.58)	0.68 (2.10)	1.75 (3.13)	
Apathy n, (%)	94 (12.5)	50 (26.9)	12 (20)	10 (35.7)	<.001
NPI mean score (SD)	0.64 (2.07)	1.59 (3.20)	1.37 (3.16)	2.59 (4.18)	
Mean number of symptoms in NPI (SD)	1.43 (1.86)	2.84 (2.56)	2.05 (2.15)	3.53 (2.49)	<.001**

Notes: Chi square test used unless otherwise stated. See other neuropsychiatric symptoms in Table S3 in supporting information.
*Fisher's exact test used where cell counts ≤5.
**Kruskal–Wallis used to determine *P* value.
Abbreviations: AD, Alzheimer's disease; AD+LBD, meets classification for AD and LBD; CDR, Clinical Dementia Rating; LBD, Lewy body disease; NP, no neuropathological diagnosis; NPI, Neuropsychiatric Inventory; SD, standard deviation.

no difference in cause of death across the groups when stratified by neuropathological diagnosis (Fisher's exact = 0.36; Table S1 in supporting information). Of patients reported to be taking psychotropic medication (5.7%; n = 60), 1.2% (n = 13) were taking antipsychotics and 3.1% (n = 33) were taking antidepressants; this is representative of epidemiological data from São Paulo.[43] Data for the use of medication across all participants is included in Table S2 in supporting information.

3.2 | Neuropathological diagnoses and neuropsychiatric symptoms

Hallucinations were the most commonly reported symptom in participants with dual AD+LBD pathology (50%), followed by depression and apathy (35.7% each), and agitation (28.6%). In all other groups (AD, LBD, and NP), depression was commonly reported (35%; 35.5%; 20.3%, respectively). Hallucinations and delusions were uncommon in the NP group (4.2% and 4%, respectively; Table 2). Sleep disturbance, appetite changes, and anxiety were also common across all groups (Table S3 in supporting information).

Models comparing LBD, AD, and AD+LBD to NP, adjusted for age, ethnicity, sex, education, cause of death, and use of antipsychotic and antidepressant medication showed significantly higher risk of developing hallucination and delusions across all diagnostic groups relative to NP. The increased risk was highest for hallucinations in the dual pathology group (relative risk ratio [RRR] [95% confidence interval (CI)] = 16.9 [7.00–40.9], $P < .001$). There were significantly greater odds of agitation and apathy in the AD and AD+LBD groups relative to the NP group. The AD and LBD groups had greater odds of depression than the NP group. All groups showed higher odds of increased burden of NPS than the NP group with the greatest number of symptoms in the AD+LBD group (RRR [95% CI] = 1.47 [1.27–1.71], $P < .001$; Table 3). Disinhibition, aberrant motor behavior, and irritability were significantly increased in the AD and dual pathology groups, Table S4 in supporting information.

If CDR was additionally adjusted for in the models the risk of developing hallucinations remained significantly higher for cases with dual AD+LBD pathology over the NP group (RRR [95% CI] = 4.32 [1.59–11.8], $P = .004$). All other differences in the risk of developing hallucinations, depression, apathy, delusions, agitation, or total number of symptoms in the NPI across the neuropathological groups became non-significant. If this analysis was restricted only to cases with CDR≥1 (AD n = 89, LBD n = 16, AD+LBD n = 20) there was no difference in the risk of developing any NPS across the groups.

3.3 | Association between neuropathological lesions and neuropsychiatric symptoms

We also examined the relationships between neuropathological substrates and NPS across all 1038 cases with diagnostic categories collapsed (Figure 2). Across the included cases 36% (n = 367) had NFT pathology with Braak stage ≥III, 24% (n = 244) had moderate or frequent Aβ neuritic plaques, 8% (n = 86) had LB Braak stage ≥III, 16.1% (n = 163) had hyaline atherosclerosis, 4% (n = 45) had CAA, 2% (n = 21) had lacunar infarcts, and 10% (n = 64) had TDP-43 proteinopathy.

In adjusted multivariable logistic regression, the odds of hallucinations were significantly increased with higher LB Braak scores (odds ratio [OR; 95% CI] = 1.27 [1.11–1.44], $P < .001$). No other neuropathological substrate was associated with hallucinations in this model (Table 4). However, unadjusted for CDR, NFT Braak stage was also associated with greater odds of hallucinations (OR [95% CI] = 1.53 [1.23–1.57], $P < .001$).

TABLE 3 Association between neuropathological diagnoses and neuropsychiatric symptoms (n = 1027)

Symptom	Neuropathological diagnostic classification	RRR (95% CI)	*P* value
Hallucination	NP	1 (reference)	
	AD	3.53 [2.04–6.12]	**<.001**
	LBD	3.91 [1.87–8.16]	**<.001**
	AD + LBD	16.9 [7.00–40.9]	**<.001**
Agitation	NP	1 (reference)	
	AD	2.63 [1.67–4.16]	**<.001**
	LBD	0.99 [0.43–2.28]	.98
	AD + LBD	3.08 [1.25–7.61]	**.02**
Depression	NP	1 (reference)	
	AD	1.92 [1.28–2.88]	**.002**
	LBD	1.89 [1.04–3.43]	**.04**
	AD + LBD	1.99 [0.87–4.55]	.10
Delusion	NP	1 (reference)	
	AD	5.02 [2.71–9.28]	**<.001**
	LBD	2.76 [1.06–7.20]	**.04**
	AD + LBD	4.98 [1.68–14.8]	**.004**
Apathy	NP	1 (reference)	
	AD	1.90 [1.21–2.98]	**.005**
	LBD	1.38 [0.68–2.77]	.37
	AD + LBD	3.25 [1.40–7.58]	**.006**
Number of symptoms in NPI	NP	1 (reference)	
	AD	1.31 [1.20–1.42]	**<.001**
	LBD	1.15 [1.01–1.31]	**.03**
	AD + LBD	1.47 [1.27–1.71]	**<.001**

Notes: Multinomial ordinal logistic regression model with neuropathological diagnosis as the dependent variable, using "NP" as the reference group, and neuropsychiatric symptom in the NPI as the independent variable. Models are adjusted for age, sex, ethnicity, years of education, use of antidepressant or psychotropic medication, and cause of death. See Table S4 in supporting information for remaining neuropsychiatric symptoms. Bold denotes p < 0.05.

Abbreviations: AD, Alzheimer's disease; AD+LBD, meets classification for AD and LBD; CDR, Clinical Dementia Rating; CI, confidence interval; LBD, Lewy body disease; NP, no neuropathological diagnosis; NPI, Neuropsychiatric Inventory; RRR, relative risk ratio.

Greater odds of depression (OR [95% CI] = 1.22 [1.05–1.43], *P* = .01) and agitation (OR [95% CI] = 1.33 [1.10–1.61], *P* = .003) were associated with higher NFT Braak score. Lacunar infarcts were associated with greater odds of delusions (OR [95% CI] = 5.87 [1.64–21.0], *P* = .007). Other neuropathological substrates such as CAA, hyaline atherosclerosis, and TDP-43 did not associate with greater odds of any of the investigated NPS (Table 4). Appetite change and irritability were significantly associated with greater NFT Braak staging (Table S5 in supporting information).

The total number of symptoms on the NPI across all the symptom domains correlated with higher Braak stage for NFT in a multivariable Poisson regression for adjusted for age, sex, ethnicity, years of education, CDR, cause of death, and use of antipsychotics and antidepressants (incidence rate ratio [IRR; 95% CI] = 1.11 [1.04–1.19], *P* = .002. Unadjusted for CDR total number of symptoms was also associated with higher LBD Braak score IRR [95% CI] = 1.08 [1.03–1.12], *P* = .001). The remaining neuropathological substrates did not correlate with the total number of symptoms on the NPI (Table 4). The interaction between AD and LB pathology for total number of symptoms on the NPI was analyzed in a multiplicative scale adjusted for age, sex, and years of education. We did not find evidence of an interaction between either PD Braak staging and AD Braak staging (coefficient = −0.20 [95% CI = -1.13 to 0.73], *P* = .67) or PD Braak staging and neuritic plaque CERAD staging (coefficient = 0.25 [95% CI = -0.72 to 1.22], *P* = .61).

4 | DISCUSSION

In this large population-based *post mortem* study, we aimed to characterize the neuropathological correlates of the most common NPS across AD and LBD. The inclusion of cases across a range of neuropathological stages, irrespective of the overarching clinicopathological diagnosis, gave insight as to how the progression of neuropathology from the earliest stages contributed to each NPS. We found higher Braak stages for LBD were associated with increased odds of developing hallucinations, independent of cognition and demographic variables. Higher staging of NFT was associated with greater overall burden of NPS, with greater odds of developing depression and agitation, echoing findings seen in AD populations.[6] A greater number of total symptoms on the NPI was associated with higher NFT Braak stages, and when unadjusted for CDR, LBD Braak stages, but we did not find interactions between LB pathology and either neuritic plaques or NFT. The dual importance of AD and LBD was illustrated when considering cases by neuropathological diagnosis; subjects with both AD and LBD pathology showed the highest burden of NPS, with the greatest number of symptoms in the NPI, in addition to the greatest risk of developing hallucinations, agitation, and apathy. This suggests there may be an additive rather than interactive synergistic relationship between these pathologies.

With the exception of hallucinations, the differences in the risk of developing NPS across neuropathological diagnoses were not seen independent of cognition. This suggests the mechanisms driving these symptoms are intrinsically linked. Indeed, cognitive impairment is a known risk factor for many NPS in AD and LBD with NPS also reciprocally associated with increased cognitive decline in dementia.[44–46] We did not find the greater burden of NPS in LBD relative to AD that has been seen in clinical studies in the prodromal stages,[47,48] this may reflect the more advanced clinical status of those with AD versus LBD in our study, with a higher proportion of CDR ≥ 1. However, it is also possible that other studies with primarily clinical diagnoses overestimate DLB in cases with NPS; it is well documented that psychotic symptoms increase the likelihood of DLB being diagnosed and so estimates of the prevalence of NPS are prone to bias without

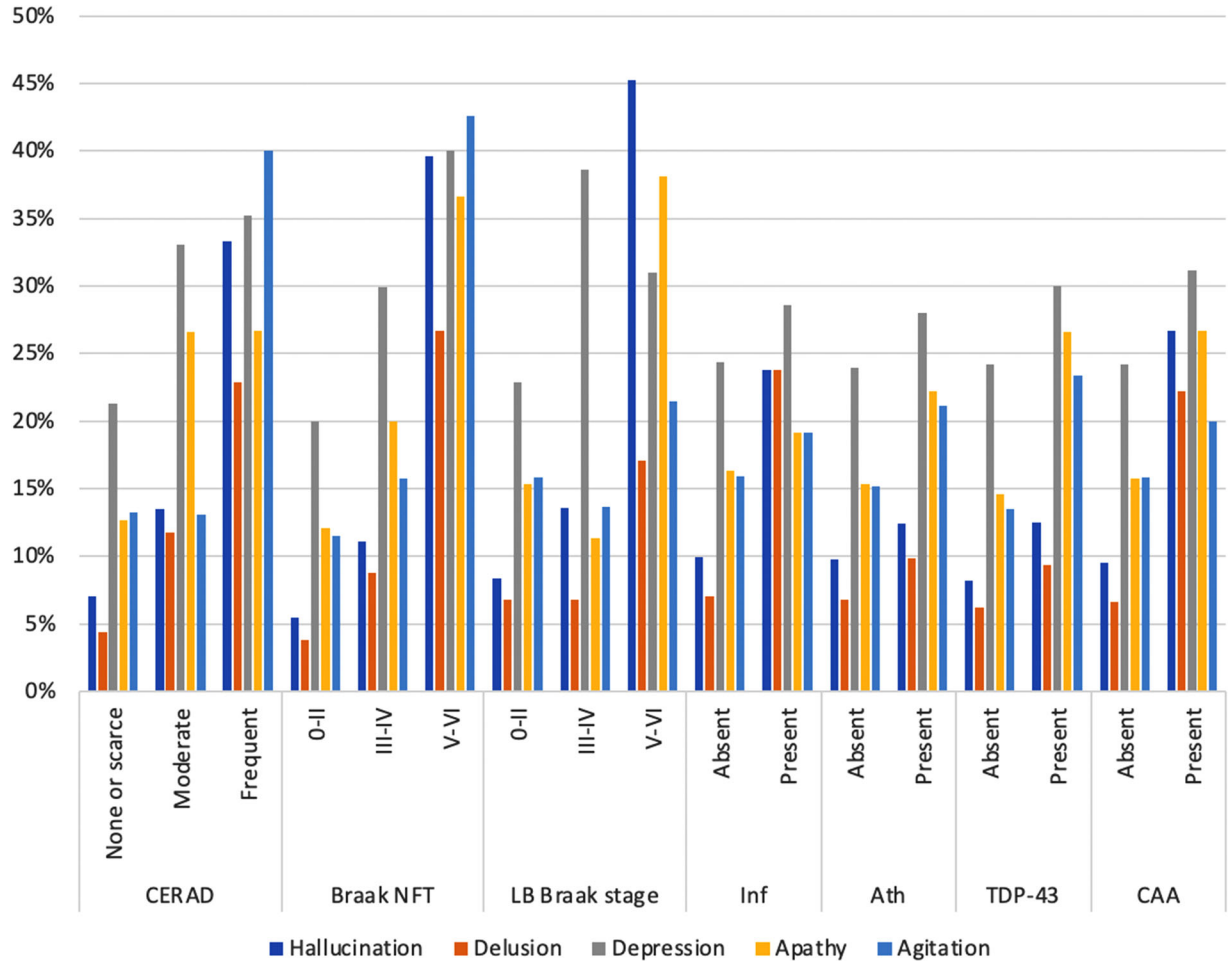

FIGURE 2 Neuropathological substrates stratified by key neuropsychiatric symptoms. Ath, hyaline atherosclerosis; CAA, cerebral amyloid angiopathy; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; Inf, lacunar infarct; LB, Lewy body; NFT, neurofibrillary tangle

additional neuropathological confirmation of diagnosis.[5,49] The differences across neuropathological groups were also eroded when the analysis was restricted to those with CDR≥ 1; it is likely that the analysis was underpowered in this smaller population but future studies should investigate whether NPS have greater discriminatory potential in the prodromal stages of dementia. Indeed, VH occurring in the first 5 years of dementia are more associated with neuropathologically confirmed LBD than AD while they are equally common across both in the later stages of the disease.[26] Furthermore, in analysis of neuropathological substrates independent of neuropathological diagnosis where CDR was controlled for, various neuropathologies were significantly associated with NPS suggesting a contribution to the etiology independent of cognitive impairment in the prodromal stages.

The etiology of NPS in dementia is clearly multifactorial, likely with different neuropathological substrates contributing to each NPS in varying degrees. Indeed, the respective etiologies likely differ to some extent between patients; while 2% without hallucinations had LB stage V/VI, two thirds of those with hallucinations in the study had LB stage 0. LBs in the cortical regions appear to be sufficient but not necessary to elicit hallucinations. LBs in frontal, limbic, and temporal areas have previously been implicated in the etiology of VH,[27,50–52] and our study suggests that it is the progression of LBD from brainstem areas to the cortex that increases the risk of developing hallucinations, particularly when combined with AD pathology. The number of cases with hallucinations increased progressively with higher LB Braak stages: 8.4% in Braak stages 0 to II (restricted to brainstem), 14% in stages III to IV, and 45% in stages V to VI (sensory association cortex involvement). This is consistent with the view that the evolution of symptoms from illusions to hallucinations in LBD may track Braak stage.[24] We did not replicate the evidence that AD pathology was individually associated with increased odds of hallucinations unless CDR was unadjusted for,[23] and we did not find evidence of a multiplicative interaction between LB and NFT or neuritic plaques suggesting the absence of a synergistic relationship. However, cases with comorbid AD+LBD pathology had the highest risk of developing hallucinations suggesting these pathologies may contribute separately in an additive way. CAA has previously been implicated in the psychotic symptoms in AD,[12] but we did not find evidence to support this. However, the degree of comorbid vascular pathology was considerably lower in the current study with only 4% of cases meeting criteria for CAA; cases with exclusively VaD or CAA without LB or AD pathology were excluded at the start of the

TABLE 4 Association between neuropathological lesions and neuropsychiatric symptoms (n = 987)

Symptom	Neuropathological variable	OR [95% CI]	*P* value
Hallucinations	Lewy body disease (Braak stage)	**1.27 [1.11–1.44]**	**<.001**
	Braak NFT stage	1.25 [0.98–1.59]	.07
	CERAD neuritic plaque score	0.93 [0.67–1.29]	.66
	Lacunar infarct	3.21 [0.92–11.2]	.07
	Cerebral amyloid angiopathy	1.85 [0.77–4.43]	.17
	Hyaline atherosclerosis	1.33 [0.72–2.47]	.37
	TDP-43 proteinopathy[a]	0.63 [0.24–1.68]	.36
Agitation	Lewy body disease (Braak stage)	0.92 [0.80–1.05]	.22
	Braak NFT stage	**1.33 [1.10–1.61]**	**.003**
	CERAD neuritic plaque score	0.82 [0.63–1.08]	.16
	Lacunar infarct	1.22 [0.35–4.32]	.75
	Cerebral amyloid angiopathy	0.75 [0.31–1.82]	.53
	Hyaline atherosclerosis	1.41 [0.86–2.30]	.17
	TDP-43 proteinopathy[a]	1.43 [0.67–3.02]	.36
Delusions	Lewy body disease (Braak stage)	0.98 [0.84–1.15]	.82
	Braak NFT stage	1.23 [0.93–1.61]	.14
	CERAD neuritic plaque score	0.97 [0.67–1.41]	.89
	Lacunar infarct	**5.87 [1.64–21.0]**	**.007**
	Cerebral amyloid angiopathy	2.52 [1.00–6.33]	.049
	Hyaline atherosclerosis	1.31 [0.65–2.61]	.68
	TDP-43 proteinopathy[a]	0.66 [0.21–2.04]	.47
Depression	Lewy body disease (Braak stage)	1.02 [0.91–1.14]	.80
	Braak NFT stage	**1.22 [1.05–1.43]**	**.01**
	CERAD neuritic plaque score	0.83 [0.66–1.03]	.10
	Lacunar infarct	1.33 [0.48–3.65]	.58
	Cerebral amyloid angiopathy	0.84 [0.39–1.77]	.64
	Hyaline atherosclerosis	1.15 [0.76–1.74]	.52
	TDP-43 proteinopathy[a]	0.77 [0.39–1.54]	.46
Apathy	Lewy body disease (Braak stage)	1.00 [0.88–1.13]	1.00
	Braak NFT stage	1.10 [0.91–1.32]	.33
	CERAD neuritic plaque score	0.77 [0.59–1.01]	.06
	Lacunar infarct	1.19 [0.36–3.96]	.78
	Cerebral amyloid angiopathy	1.16 [0.51–2.66]	.72
	Hyaline atherosclerosis	1.42 [0.88–2.29]	.15
	TDP-43 proteinopathy[a]	1.34 [0.67–2.68]	.41
Total number of symptoms on NPI[b]	Lewy body disease (Braak stage)	**1.08 [1.03–1.12]**	**.001**
	Braak NFT stage	**1.22 [1.14–1.30]**	**<.001**
	CERAD neuritic plaque score	1.03 [0.93–1.13]	.59
	Lacunar infarct	1.15 [0.83–1.59]	.39
	Cerebral amyloid angiopathy	1.02 [0.76–1.37]	.90
	Hyaline atherosclerosis	1.16 [0.93–1.44]	.06
	TDP-43 proteinopathy[a]	1.22 [0.91–1.63]	.19

Notes: Multivariable logistic regression for neuropsychiatric symptoms by neuropathological substrate. Models adjusted for age, sex, ethnicity, years of education, CDR, cause of death, and antidepressant or psychotropic medication use. Bold denotes $p < 0.05$.

[a]n = 578.

[b]Multivariable Poisson regression for total number of symptoms on NPI by neuropathological substrate with IRR (incidence rate ratio). Adjusted for age, sex, ethnicity, years of education, cause of death, and antidepressant or psychotropic medication use. See Table S5 in supporting information for remaining neuropsychiatric symptoms.

Abbreviations: CERAD, Consortium to Establish a Reference for Alzheimer's Disease; CI, confidence interval NFT, neurofibrillary tangle; NPI, Neuropsychiatric Inventory; OR, odds ratio.

study. Therefore, our study may have been underpowered to find a relationship between CAA and psychotic symptoms.

The Braak progression of NFT is associated with increased odds of agitation and depression, corresponding to known anatomical and functional correlates of these NPS. The early accumulation of NFT in the locus coeruleus, disrupting the noradrenaline producing neurons, has been hypothesized to underlie the increased agitation in early Braak stages,[6,53,54] while volumetric loss in cortical areas including the frontal cortex and limbic areas are also correlated with agitation.[55,56] These dual, consecutive, processes could account for the increasing odds of agitation with Braak progression from 0 to VI, contributing to the biological basis of NPS in AD (and LBD where even early stage AD pathology co-exists), initiated in the pre-cognitive stages. Depression has also been associated with increased cortical NFT in a number of large clinicopathological studies of AD[57,58] and the current study illustrates the importance of NFT in the etiology of depression, independent of clinicopathological diagnosis. We suggest that the odds of depression increasing with progression of NFT throughout the brainstem into the cortex likely reflects disruption to the locus coeruleus and dorsal raphe nuclei in early stages[59] with additive NFT accumulation and atrophy in the temporal and cingulate cortices in later Braak stages.[60–62] We did not demonstrate an association between LB pathology and agitation or depression, despite the known degeneration of the locus coeruleus in LBD.[63] This may reflect the earlier stage of clinical disease in the LBD patients with only 27% with CDR≥1. However, all LBD patients met the neuropathological criteria with PD Braak staging ≥III and therefore despite their earlier clinical stage they were not without a significant LB burden. It seems likely that location of the pathology, such as inclusion of specific nuclei like the locus coeruleus, is an important additional factor to consider in the etiology of NPS which may not be fully captured in the staging of pathology.[27] This will be an important consideration for future studies.

There are a number of limitations to be noted in the current study. Cross-sectional neuropathological studies are inherently correlational without opportunity to characterize longitudinal relationships with NPS. However, while many such studies are criticized for including exclusively late-stage dementia patients, our large population-based study includes all consenting cases with a non-traumatic cause of death, with consequently a wide range of neuropathological outcomes and clinical stages. Furthermore, neuropathology remains the gold standard for staging AD and LBD as clinical assessments are fraught with misdiagnoses and lack the sensitivity and specificity of neuropathological analysis.[49]

A second limitation of the current study was the use of the Braak staging for LB pathology. Newer classifications such as the LB pathology consensus (LPC) criteria now exist, with greater inter-rater reliability and more successful classification of cases.[64] While use of LB Braak staging in our study allowed associations between NPS and the progression of LB into the cortex to be identified, future studies should consider using the newer criteria. In addition, future studies should adopt the newest criteria for staging AD and TDP-43 proteinopathies.

In our study, fewer of the neuropathologically classified LBD met criteria for dementia (CDR ≥ 1) than in the AD and AD+LBD groups. This suggests that a higher proportion meeting neuropathological criteria for LBD were in the prodromal or clinically silent phase of the disease, which may underlie the relatively lower burden of NPS seen in the LBD group. However, in the analysis across neuropathological variables independent of neuropathological diagnosis CDR was controlled for, suggesting the substrates do contribute to NPS in addition to cognitive impairment. The characterization of NPS in this study relied on the NPI-Q and therefore lacked information such as the type of hallucinations. Future studies should aim to include measures with greater phenomenological detail of NPS. A final weakness of our study relates to its vulnerability to informant recall bias with the clinical data collected immediately *post mortem* for the period 3 months prior to death. To minimize potential bias, informants are required to have had close weekly contact with the deceased in the 6 months prior to their death. The semi-structured interview has been validated for clinical dementia ratings associated with NPI,[39,65] but to further reduce the influence of recall bias, all NPS were included in the analysis on a binary basis, thus being less subjective and open to recall bias. While we believe the influence of such bias would be more likely to undermine the strength of any associations, nevertheless this will need to be supported in future studies.

The unique strength of this population-based study lies in its ability to capture, with systematic NPS assessment, the impact of mild but potentially clinically relevant neuropathology, which would be neglected in studies with clinical cohorts, limited to end-stage disease, or using brain banks. We were able to explore the impact of individual neuropathologies, independent of diagnosis, to assess contributions to the clinical phenotype of NPS.

We identify an increased risk for NPS associated with NFT and LB pathology. Our study extends previous findings showing an association between AD pathology and NPS and highlights the potential for other neuropathological substrates to contribute to clinical phenotype across the diagnostic criteria, emphasized by the greatest symptomatic burden being seen in those with dual pathology. Our results underscore the complex, multifactorial contribution of neuropathology to NPS. Better understanding of the pathophysiology driving NPS will facilitate earlier diagnosis and more effective treatment of these common and disabling symptoms.

ACKNOWLEDGMENTS

L.L.G. is funded by the Alzheimer's Society. L.T.G. is sponsored by NIH K24053435. D.F., R.L., R.F.R., C.P., R.N., and W.J.F. have nothing to declare. R.R. is supported by an Alzheimer's Association Research Fellowship. R.N. is supported by the Alzheimer's Association and Brazilian National Council for Scientific and Technological Development. He is on the advisory board for Biogen. D.A. has received research support and/or honoraria from Astra-Zeneca, H. Lundbeck, Novartis Pharmaceuticals, Evonik, and GE Health and has served as paid consultant for H. Lundbeck, Eisai, Heptares, Mentis Cura, Eli Lilly, and Biogen. C.K.S. is funded by the Alzheimer's Association (AARG-20-678884)

CONFLICTS OF INTEREST

Author disclosures are available in the supporting information.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Gibson LL, Grinberg LT, ffytche D, et al. Neuropathological correlates of neuropsychiatric symptoms in dementia. *Alzheimer's Dement*. 2023;19:1372–1382. https://doi.org/10.1002/alz.12765