Title

Neuropathological correlates of neuropsychiatric symptoms in dementia.

Journal

Alzheimers & Dementia: The Journal of the Alzheimers Association, 19(4)

Authors

Ffytche, Dominic
Leite, Renata
Rodriguez, Roberta
et al.

Publication Date

2023-04-01

DOI

10.1002/alz.12765

Peer reviewed

HHS Public Access

Author manuscript

Alzheimers Dement. Author manuscript; available in PMC 2024 April 01.

Published in final edited form as:

Alzheimers Dement. 2023 April ; 19(4): 1372–1382. doi:10.1002/alz.12765.

Neuropathological correlates of neuropsychiatric symptoms in dementia

Lucy L. Gibson, MRCPsych[1], **Lea T. Grinberg, MD PhD**[2,3], **Dominic ffytche**[1], **Renata E. P. Leite, PhD**[3], **Roberta D. Rodriguez**[3], **Renata E. L. Ferretti-Rebustini, BSN, RN, CNS, PhD**[3], **Carlos A. Pasqualucci, MD PhD**[3], **Ricardo Nitrini, MD PhD**[3], **Wilson Jacob-Filho, MD PhD**[3], **Dag Aarsland, MD**[1,4], **Claudia K. Suemoto, MD PhD MSc**[3]

[1]Old Age Psychiatry Department, Institute of Psychiatry, Psychology and Neuroscience, King's College London, SE5 8AF

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

[3]University of Sao Paulo Medical School

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

Abstract

INTRODUCTION—Neuropsychiatric symptoms (NPS) are very common in Lewy body disease (LBD), but their aetiology is poorly understood.

METHODS—In a population-based post-mortem study neuropathological data was collected for Lewy body (LB) neuropathology, neurofibrillary tangles (NFT), amyloid-β burden, TDP-43, lacunar infarcts, cerebral amyloid angiopathy (CAA) and hyaline atherosclerosis. Post-mortem interviews collected systematic information regarding NPS and cognitive status. 948 cases were included: (1) No pathology (NP)(n=678); (2) Alzheimer's Disease (AD)(n=183); (3) Lewy body disease (LBD)(n=57); (4) AD+LBD(n=30).

RESULTS—Hallucinations were associated with higher LB Braak stages, while higher NFT Braak staging was associated with depression, agitation and greater overall NPI score. A multiplicative interaction was seen between AD and LB pathologies and cases with dual pathology had the highest relative risk of hallucinations, agitation, apathy and total NPI score.

DISCUSSION—LB and AD pathology contribute differentially to NPS with a synergistic interaction likely contributing to the increased burden of NPS.

Keywords

Neuropsychiatric symptoms; Lewy Body Disease; neuropathology

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

Introduction

LBD is a neurocognitive disorder with prominent motor symptoms which includes Parkinson's disease dementia (PDD) and dementia with Lewy bodies (DLB). Collectively, this is the second most common neurodegenerative dementia after AD characterised neuropathologically by the accumulation of aggregated alpha-synuclein in 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 NPS at some point in the disease course with depression, agitation, apathy and psychosis being particularly common (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).

Early in PD, minor hallucinations such as illusions, passage and presence hallucinations often appear, progressing over time to formed visual hallucinations (VH) and later, hallucinations in other modalities (6, 7). The timing and risk factors for this progression mirrors the Braak progression of LBD pathology from brainstem to forebrain suggesting an aetiological link (6). However, to our knowledge, no study to date has demonstrated a clear association between PD Braak progression and increasing severity of hallucinations. VH have been associated with higher LB load in the limbic regions, in addition to the frontal, temporal and parietal regions where the burden of amyloid and tau also may also have an impact (8–10). However, in neuropathological studies of AD, the incidence of psychosis has been found to relate to LBD and vascular risk factors rather than AD pathology (11). Where VH occur in the absence of dementia, common in PD, LB pathology is not seen in the cortex suggesting that the neuropathological mechanisms underpinning VH can be separated from dementia-related processes (12).

A number of studies have examined the neural correlates of NPS in AD but this remains relatively unexplored in LBD (13). In AD, increased NFT and burden of hyperphosphorylated tau have been associated with psychosis, agitation and depression (13, 14), while co-morbid LBD pathology is associated with increased anxiety and irritability (15). Clinicopathological studies have shown that more than half of patients with DLB have co-existent AD pathology with accelerated cognitive decline and shorter survival times (16, 17). However, the impact of this dual pathology, and other age-related neuropathologies, on the NPS in LBD is unknown. To date, advanced small vessel disease (SVD) and cerebral amyloid angiopathy (CAA) have been associated with psychosis in AD, but not DLB (18) and TDP-43 proteinopathy has been reported in up to 60% of DLB subjects (19) with unclear implications for NPS (15).

We aimed to investigate neuropathological correlates of five clinically important and common neuropsychiatric symptoms (hallucinations, delusions, depression, apathy and agitation) (4), independent of the overarching neuropathological diagnosis. Neuropathological studies are often limited to highly selected cohorts with end-stage disease and small sample sizes. The Biobank for Aging Studies (BAS) is a unique population-based cohort which includes cases with a wide range of neuropathological outcomes and clinical

stages allowing the impact of low burden NFT, Amyloid-β and LB to be assessed (20). 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 between these pathologies akin to cognitive impairment.

MATERIALS AND METHODS

Patient cohort

We used cases collected between 2004 and 2021 from the BAS of the University of Sao Paulo, Brazil. In São Paulo, autopsy is mandatory where cause of death is unclear and non-traumatic. 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 six months prior to death, and ability of next of kin to provide clinical information and consent to brain donation. BAS exclusion criteria includes brain tissue not suitable for neuropathological analyses (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.

For the purposes of this study, we included all participants who exhibited AD-type pathology (plaques and/or NFTs), LBD, or who were without sufficient pathology to fulfil a disease diagnosis in neuropathological evaluation. Cases with a diagnosis of cerebrovascular pathology (VaD) (n=133), defined as such by the presence of one large chronic infarct (>1cm) or three lacunae (<1cm), 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 informed consent.

Neuropathological assessment

The BAS uses a 14-region immunohistochemistry panel to detect neurodegeneration and universally-accepted criteria to stage and diagnose cases (20, 21). NFT were assessed in formalin-fixed paraffin-embedded sections by immunostaining for phospho-Ser396/Ser404 tau scored by Braak stage (0, I/II, III/IV and V/VI) following conventional categorization (22, 23). Amyloid-β pathology was scored using CERAD-NP for the density of neuritic plaques (none, sparse, moderate or frequent) (24). LB neuropathology was classified using the Braak staging 0-VI for PD (25). Immunohistochemistry for transactive response DNA-binding protein 43 kDA (TDP-43) was introduced into the protocol in 2012 with a binary classification (26). Cerebrovascular lesions were assessed by gross macroscopic evaluation of the whole brain and microscopic evaluation of the 14 regions using haematoxylin-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 (27). CAA was considered present where widespread disease was seen in ≥3 different cortical areas (27).

Neuropathological diagnostic classification

A neuropathological diagnosis of AD was made for individuals with Alzheimer’s Braak stage III or above in addition to a CERAD neuritic plaque density of moderate or frequent.

LBD was diagnosed neuropathologically where cases had a Parkinson's Braak classification for of III or greater. 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. For the dual pathology 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).

Evaluation of symptoms

The deceased's clinical history was obtained from a knowledgeable informant in a semi-structured interview, which has previously been validated for post-mortem use (28). The clinical interview includes information regarding sociodemographics, cognitive evaluation using the informant section of the Clinical Dementia Rating Scale (CDR), which has been validated in the Brazilian population (28, 29) and the Neuropsychiatric Inventory (30). Scores from the CDR and 12-item NPI collected in postmortem informant interviews reflect the participant's status three months before death to avoid influence of peri-agonal events (31). The NPI evaluates 12 domains: agitation, apathy, anxiety, appetite, delusions, depression, disinhibition, elation, hallucinations, irritability, motor, 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 our participants are zero, this was set as the cutoff for a negative diagnosis, with any score above zero receiving a positive diagnosis.

Statistics

One-way ANOVA 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. Multivariable ordinal logistic regression models assessed the odds of having hallucinations, agitation, apathy, depression and delusions for the given pathologic groups (AD, LBD, AD+LBD) compared to reference group (NP). Models were adjusted for age, sex, ethnicity and years of education. For total NPI score 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 neuropsychiatric symptoms outside the diagnostic classification criteria, this analysis was performed across all 948 cases with diagnostic categories collapsed. Thus cases with mild but potentially clinically relevant neuropathology, such as lower staging for NFT, Amyloid-β and LB, were included in the analysis. Multivariable logistic regression was performed with presence of hallucinations, delusions, agitation, apathy, or depression as the binary dependent variable and the neuropathological substrates: LBD (PD Braak staging), NFT staging (AD Braak staging), CERAD neuritic plaque score, 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, and CDR score. TDP-43 was included in a separate model due to the reduced number of subjects (n=474). We explored the multiplicative interaction effects between Braak PD and

both Braak AD and CERAD amyloid-β. Poisson multiple linear regression was performed for total NPI score and neuropathological substrates, adjusted for age, sex, ethnicity, years of education, and CDR score.

RESULTS

Demographic information

948 cases were included in total of mean age 72.9 (SD 12.2), 48.6% of the participants were female and the mean educational level was 4.6 years (SD = 3.9); broadly representative of the death data from Sao Paulo city (20). Regarding ethnicity, 68% of cases were identified by their next of kin as White, 11% as Black, 17% as mixed and 2% as other. This demographic composition is overall similar to the Sao Paulo 2010 census but the mixed population was underrepresented (26.5%) and Black population (5.5%) overrepresented.

Cases were classified by neuropathological diagnosis: 678 (71.5%) of included participants did not have sufficient neuropathological changes to meet a disease classification (NP), 183 (19%) were diagnosed with AD, 57 (6%) with LBD and 30 (3%) met the neuropathological criteria for both LBD and AD. Demographic data stratified by neuropathological diagnosis is shown in Table 1.

Neuropathological diagnoses and neuropsychiatric symptoms

Hallucinations were the most commonly reported symptom in participants with dual AD+LBD pathology (51.7%), followed by depression and apathy (34.5% each), agitation (27.6%) with delusions as the least commonly reported symptom amongst this group (17.2%). In all other groups (AD, LBD and NP), depression was the most commonly reported symptom (32.4%; 35.1%; 20% respectively). Hallucinations and delusions were uncommon in the NP group (4.2% and 3% respectively) (Table 2).

Models comparing LBD, AD and dual pathology AD+LBD to NP, adjusted for age, ethnicity, sex, and education level, showed significantly higher risk of developing hallucination and delusions across all diagnostic groups compared to NP. The increased risk was highest for hallucinations in the dual pathology group (RRR, [95% CI] = 19.3 [8.00–46.3], p <0.001). 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 greater odds of higher burden of NPS than the NP group with the risk of increased total NPI score and number of symptoms in the NPI highest in the AD+LBD group (RRR [95% CI] = 1.04 [1.02–1.06], p <0.001; RRR [95% CI] = 1.43 [1.23–1.65], p <0.001). (Table 3).

If CDR was additionally adjusted for in the models the relative risk of developing hallucinations remained significantly higher for cases with dual AD+LBD pathology over the NP group (RRR = 2.89 [95% CI 1.63–13.1], p=0.004). All other differences in the relative risk of developing hallucinations, depression, apathy, delusions, agitation or total NPI score across the neuropathological groups became non-significant. If this analysis was restricted only to cases with CDR≥1 (AD n=82, LBD n=14, AD+LBD n=21) there was no

difference in the relative risk of developing any of the neuropsychiatric symptoms across the groups.

Association between neuropathological lesions and neuropsychiatric symptoms

We also examined the relationships between neuropathological substrates and neuropsychiatric symptoms across all 948 cases with diagnostic categories collapsed (Figure 2). Across the included cases 37% (n=347) had NFT pathology with Braak stage III or greater, 25% (n=235) had moderate or frequent beta-amyloid neuritic plaques, 9% (n=86) had LB Braak stage III or greater, 12% (n=116) had hyaline atherosclerosis, 4% (n=40) had cerebral amyloid angiopathy and 11% (n=52) had TDP-43 pathology.

In multivariable logistic regression, adjusted for age, sex, ethnicity, CDR and years of education, the odds of hallucinations were significant increased with higher LB Braak scores (OR, [95% CI] = 1.30 [1.13–1.49], $p < 0.001$). No other neuropathological substrate was associated with greater odds of hallucinations (Table 4).

The models showed greater odds of depression (OR, [95% CI] = 1.28 [1.09–1.50], $p < 0.001$) and agitation (OR, [95% CI] = 1.30 [1.07–1.57], $p = 0.009$) with higher Braak score for NFT. Lacunar infarcts were associated with greater odds for delusions (OR, [95% CI] = 4.68 [1.12–19.5], $p = 0.03$). More frequent CERAD neuritic plaques was associated with lower odds for apathy (OR, [95% CI] = 0.70 [0.52–0.93], $p = 0.01$). Other neuropathological substrates such as CAA, hyaline atherosclerosis, and TDP-43 did not associate with greater odds of any of the investigated neuropsychiatric symptoms (Table 4).

The total score on the NPI across all the symptom domains correlated with higher Braak stage for neurofibrillary tangles in a multivariable Poisson regression for adjusted for age, sex, ethnicity, years of education and CDR (IRR, [95% CI] = 1.15 [1.05–1.27], $p = 0.004$). The remaining neuropathological substrates did not correlate with the total NPI score (Table 4). The interaction between AD and LB pathology for total NPI score was also analysed in a multiplicative scale adjusted for age, sex and years of education. There was a significant interaction between both PD Braak staging and AD Braak staging (Coefficient = 5.22, [95% CI 1.19–9.26], $p = 0.01$) and PD Braak staging and neuritic plaque CERAD staging (Coefficient = 4.93 [95% CI 0.38–9.49], $p = 0.03$).

DISCUSSION

In this large population based post-mortem study, we aimed to characterise 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 contributed to each NPS. We found higher Braak stages for LB pathology 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 populations of exclusively AD (13). The significant interaction between LB pathology and both amyloid neuritic plaques and NFT was indicates a synergistic relationship between

these pathologies. Indeed, the dual importance of AD and LBD was also illustrated when considering cases by neuropathological diagnosis; subjects with both AD and LBD pathology showed the highest burden of NPS, with the highest NPI score and number of different symptoms in the NPI, in addition to the greatest risk of developing hallucinations, agitation, and apathy.

With the exception of hallucinations, the differences in the risk of developing NPS across neuropathological diagnostic categories 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 (32–34). We also did not find the greater burden of NPS in LBD relative to AD that has been found in previous clinical studies in the prodromal stages (35, 36), this may reflect the more advanced clinical status of those with neuropathological diagnosis of AD relative to LBD in our study, with a higher proportion of CDR ≥ 1. However, it is also possible that other studies with primarily clinical diagnoses overestimate LB dementias in cases with NPS; it is well documented that psychotic symptoms increase the likelihood of DLB being diagnosed which make estimates of the prevalence of NPS prone to bias without additional neuropathological confirmation of diagnosis (5, 37). The differences across neuropathological groups were also eroded when the analysis was restricted to those with CDR≥ 1, this may reflect the smaller sample size of this population but also indicates that NPS may have more potential as discriminatory factors in the prodromal stages.

The aetiology of neuropsychiatric symptoms in dementia is clearly multifactorial, likely with different neuropathological substrates contributing to each NPS to varying degrees. Indeed, the respective aetiologies likely differ to some extent between patients; while under 3% of without hallucinations had LB stage V/VI, almost 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 limbic and temporal areas have previously been implicated in the aetiology of VH (9, 10, 12, 38), and our study suggests that it is the progression of LB from brainstem areas to the cortex that increases the risk of developing hallucinations. The number of cases with hallucinations increased progressively with higher LB Braak stages: 7.5% in Braak stages 0-II, 14% in stages III-IV and 45% in stages V-VI. We did not replicate the evidence that AD pathology individually is associated with increased odds of hallucinations (8). However, cases with comorbid AD+LBD pathology had the highest risk of developing hallucinations and we also found a significant interaction between LB Braak stages and both NFT and neuritic plaques suggesting a synergistic process occurring between these LB and AD pathologies. CAA has previously been implicated in the psychotic symptoms in AD (18), 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 vascular dementia or cerebral amyloid angiopathy without LB or AD pathology were excluded at the start of the 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 hypothesised to underlie the increased agitation in early Braak stages (13, 39, 40), while volumetric loss in cortical areas including the frontal cortex and limbic areas are also correlated with agitation (41, 42). These dual, consecutive, processes could account for the increasing odds of agitation as the Braak stage progresses 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 (43, 44) and the current study illustrates the importance of NFT in the aetiology 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 (45) with additive NFT accumulation and atrophy in the temporal and cingulate cortices in later Braak stages (46–48).

The inverse association between amyloid and apathy was an unexpected finding. This may reflect that apathy is often present in the early stages of dementia before other symptoms such as hallucinations and agitation emerge in the later stages (13). Apathy may become harder for family members to detect and grade when overshadowed by other positive NPS experienced by patients. Indeed, rates of apathy were lower in this study than is often reported in AD and DLB (49) which may reflect the lower sensitivity the NPI-informant for apathy in the context of other symptoms. The relationship between apathy and neuropathology remains unclear – a number of studies have implicated NFT and beta-amyloid pathology, but this has not been consistently seen (48, 50, 51). Mixed pathologies, such as LB and vascular changes, have also been implicated but we did not find evidence for this (13, 52).

There are a number of limitations to be noted in the current study. Cross-sectional neuropathological studies are inherently correlational without opportunity to characterise longitudinal relationships with NPS. However, while many such studies are criticised for including exclusively late-stage dementia patients, our large population-based study includes all consenting cases who underwent autopsy due to non-traumatic cause of death, with consequently 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 (37).

A second limitation of the current study was the use of the Braak Parkinsonian staging for LB pathology. Newer classifications such as the Lewy body pathology consensus (LPC) criteria now exist, with greater inter-rater reliability and more successful classification of cases (53). The LPC is largely based on the McKeith system but scoring is dichotomous and includes amygdala-predominant and olfactory-only stages. 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 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 characterisation of NPS in this study relied on the NPI and therefore lacked information such as the modality and type of hallucinations and delusional content. 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 post-mortem. However, in order to minimise this potential bias, informants are required to have had close weekly contact with the deceased in the six months prior to their death. 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 utilising 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 findings extends the previous findings on the association between AD pathology and NPS and highlights the potential for other neuropathological substrates to contribute to clinical phenotype across the diagnostic criteria, emphasised 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.

Acknowledgements and Disclosures

LLG is funded by the Alzheimer’s Society.

LTG is sponsored by NIH K24053435

DA 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.

REFERENCES

1. Outeiro TF, Koss DJ, Erskine D, Walker L, Kurzawa-Akanbi M, Burn D, et al. Dementia with Lewy bodies: an update and outlook. Mol Neurodegener. 2019;14(1):5. [PubMed: 30665447]
2. Ballard C, Ziabreva I, Perry R, Larsen JP, O’Brien J, McKeith I, et al. Differences in neuropathologic characteristics across the Lewy body dementia spectrum. Neurology. 2006;67(11):1931–4. [PubMed: 17159096]
3. Aarsland D, Bronnick K, Ehrt U, De Deyn PP, Tekin S, Emre M, et al. Neuropsychiatric symptoms in patients with Parkinson’s disease and dementia: frequency, profile and associated care giver stress. J Neurol Neurosurg Psychiatry. 2007;78(1):36–42. [PubMed: 16820421]

4. Vik-Mo AO, Giil LM, Borda MG, Ballard C, Aarsland D. The individual course of neuropsychiatric symptoms in people with Alzheimer's and Lewy body dementia: 12-year longitudinal cohort study. Br J Psychiatry. 2020;216(1):43–8. [PubMed: 31506117]
5. Fischer CE, Qian W, Schweizer TA, Ismail Z, Smith EE, Millikin CP, et al. Determining the impact of psychosis on rates of false-positive and false-negative diagnosis in Alzheimer's disease. Alzheimers Dement (N Y). 2017;3(3):385–92. [PubMed: 29067344]
6. Ffytche DH, Creese B, Politis M, Chaudhuri KR, Weintraub D, Ballard C, et al. The psychosis spectrum in Parkinson disease. Nat Rev Neurol. 2017;13(2):81–95. [PubMed: 28106066]
7. Vignando M, Ffytche D, Lewis SJG, Lee PH, Chung SJ, Weil RS, et al. Mapping brain structural differences and neuroreceptor correlates in Parkinson's disease visual hallucinations. Nat Commun. 2022;13(1):519. [PubMed: 35082285]
8. Jacobson SA, Morshed T, Dugger BN, Beach TG, Hentz JG, Adler CH, et al. Plaques and tangles as well as Lewy-type alpha synucleinopathy are associated with formed visual hallucinations. Parkinsonism Relat Disord. 2014;20(9):1009–14. [PubMed: 25027359]
9. Papapetropoulos S, McCorquodale DS, Gonzalez J, Jean-Gilles L, Mash DC. Cortical and amygdalar Lewy body burden in Parkinson's disease patients with visual hallucinations. Parkinsonism Relat Disord. 2006;12(4):253–6. [PubMed: 16368258]
10. Gallagher DA, Parkkinen L, O'Sullivan SS, Spratt A, Shah A, Davey CC, et al. Testing an aetiological model of visual hallucinations in Parkinson's disease. Brain. 2011;134(Pt 11):3299–309. [PubMed: 21921019]
11. Fischer CE, Qian W, Schweizer TA, Millikin CP, Ismail Z, Smith EE, et al. Lewy Bodies, Vascular Risk Factors, and Subcortical Arteriosclerotic Leukoencephalopathy, but not Alzheimer Pathology, are Associated with Development of Psychosis in Alzheimer's Disease. J Alzheimers Dis. 2016;50(1):283–95. [PubMed: 26682680]
12. Harding AJ, Broe GA, Halliday GM. Visual hallucinations in Lewy body disease relate to Lewy bodies in the temporal lobe. Brain. 2002;125(Pt 2):391–403. [PubMed: 11844739]
13. Ehrenberg AJ, Suemoto CK, Franca Resende EP, Petersen C, Leite REP, Rodriguez RD, et al. Neuropathologic Correlates of Psychiatric Symptoms in Alzheimer's Disease. J Alzheimers Dis. 2018;66(1):115–26. [PubMed: 30223398]
14. Murray PS, Kirkwood CM, Gray MC, Fish KN, Ikonomovic MD, Hamilton RL, et al. Hyperphosphorylated tau is elevated in Alzheimer's disease with psychosis. J Alzheimers Dis. 2014;39(4):759–73. [PubMed: 24270207]
15. Bayram E, Shan G, Cummings JL. Associations between Comorbid TDP-43, Lewy Body Pathology, and Neuropsychiatric Symptoms in Alzheimer's Disease. J Alzheimers Dis. 2019;69(4):953–61. [PubMed: 31127776]
16. Sabbagh MN, Adler CH, Lahti TJ, Connor DJ, Vedders L, Peterson LK, et al. Parkinson disease with dementia: comparing patients with and without Alzheimer pathology. Alzheimer Dis Assoc Disord. 2009;23(3):295–7. [PubMed: 19812474]
17. Abdelnour C, van Steenoven I, Londos E, Blanc F, Auestad B, Kramberger MG, et al. Alzheimer's disease cerebrospinal fluid biomarkers predict cognitive decline in lewy body dementia. Mov Disord. 2016;31(8):1203–8. [PubMed: 27296778]
18. Vik-Mo AO, Bencze J, Ballard C, Hortobagyi T, Aarsland D. Advanced cerebral amyloid angiopathy and small vessel disease are associated with psychosis in Alzheimer's disease. J Neurol Neurosurg Psychiatry. 2019;90(6):728–30. [PubMed: 30054314]
19. McAleese KE, Walker L, Erskine D, Thomas AJ, McKeith IG, Attems J. TDP-43 pathology in Alzheimer's disease, dementia with Lewy bodies and ageing. Brain Pathol. 2017;27(4):472–9. [PubMed: 27495267]
20. Suemoto CK, Ferretti-Rebustini RE, Rodriguez RD, Leite RE, Soterio L, Brucki SM, et al. Neuropathological diagnoses and clinical correlates in older adults in Brazil: A cross-sectional study. PLoS Med. 2017;14(3):e1002267. [PubMed: 28350821]
21. Grinberg LT, Ferretti REL, Leite REP, Farfel JM, Pacheco SP, Alho A, et al. Clinicopathological correlates of Alzheimer's disease in a general autopsy series from Brazil. Dement Neuropsychol. 2007;1(4):356–60. [PubMed: 29213411]

22. Braak H, Braak E. Neuropathological stageing of Alzheimer-related changes. Acta Neuropathol. 1991;82(4):239–59. [PubMed: 1759558]
23. Braak H, Alafuzoff I, Arzberger T, Kretzschmar H, Del Tredici K. Staging of Alzheimer disease-associated neurofibrillary pathology using paraffin sections and immunocytochemistry. Acta Neuropathol. 2006;112(4):389–404. [PubMed: 16906426]
24. 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(4):479–86. [PubMed: 2011243]
25. 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. Neurobiol Aging. 2003;24(2):197–211. [PubMed: 12498954]
26. Cairns NJ, Neumann M, Bigio EH, Holm IE, Troost D, Hatanpaa KJ, et al. TDP-43 in familial and sporadic frontotemporal lobar degeneration with ubiquitin inclusions. Am J Pathol. 2007;171(1):227–40. [PubMed: 17591968]
27. Grinberg LT, Thal DR. Vascular pathology in the aged human brain. Acta Neuropathol. 2010;119(3):277–90. [PubMed: 20155424]
28. Ferretti REL, Damin AE, Brucki SMD, Morillo LS, Perroco TR, Campora F, et al. Post-Mortem diagnosis of dementia by informant interview. Dement Neuropsychol. 2010;4(2):138–44. [PubMed: 29213677]
29. Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. Neurology. 1993;43(11):2412–4.
30. Camozzato AL, Kochhann R, Simeoni C, Konrath CA, Pedro Franz A, Carvalho A, et al. Reliability of the Brazilian Portuguese version of the Neuropsychiatric Inventory (NPI) for patients with Alzheimer's disease and their caregivers. Int Psychogeriatr. 2008;20(2):383–93. [PubMed: 18257965]
31. Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. Neurology. 1994;44(12):2308–14. [PubMed: 7991117]
32. Fenelon G, Mahieux F, Huon R, Ziegler M. Hallucinations in Parkinson's disease: prevalence, phenomenology and risk factors. Brain. 2000;123 (Pt 4):733–45. [PubMed: 10734005]
33. Paulsen JS, Salmon DP, Thal LJ, Romero R, Weisstein-Jenkins C, Galasko D, et al. Incidence of and risk factors for hallucinations and delusions in patients with probable AD. Neurology. 2000;54(10):1965–71. [PubMed: 10822438]
34. Aarsland D, Andersen K, Larsen JP, Lolk A, Kragh-Sorensen P. Prevalence and characteristics of dementia in Parkinson disease: an 8-year prospective study. Arch Neurol. 2003;60(3):387–92. [PubMed: 12633150]
35. Liu C, Liu S, Wang X, Ji Y. Neuropsychiatric profiles in mild cognitive impairment with Lewy bodies. Aging Ment Health. 2021;25(11):2011–7. [PubMed: 32896168]
36. Donaghy PC, Ciafone J, Durcan R, Hamilton CA, Barker S, Lloyd J, et al. Mild cognitive impairment with Lewy bodies: neuropsychiatric supportive symptoms and cognitive profile. Psychol Med. 2020:1–9.
37. Thomas AJ, Mahin-Babaei F, Saidi M, Lett D, Taylor JP, Walker L, et al. Improving the identification of dementia with Lewy bodies in the context of an Alzheimer's-type dementia. Alzheimers Res Ther. 2018;10(1):27. [PubMed: 29490691]
38. Kalaitzakis ME, Christian LM, Moran LB, Graeber MB, Pearce RK, Gentleman SM. Dementia and visual hallucinations associated with limbic pathology in Parkinson's disease. Parkinsonism Relat Disord. 2009;15(3):196–204. [PubMed: 18602855]
39. Weinshenker D. Long Road to Ruin: Noradrenergic Dysfunction in Neurodegenerative Disease. Trends Neurosci. 2018;41(4):211–23. [PubMed: 29475564]
40. Morris LS, McCall JG, Charney DS, Murrough JW. The role of the locus coeruleus in the generation of pathological anxiety. Brain Neurosci Adv. 2020;4:2398212820930321. [PubMed: 32954002]

41. Tekin S, Mega MS, Masterman DM, Chow T, Garakian J, Vinters HV, et al. Orbitofrontal and anterior cingulate cortex neurofibrillary tangle burden is associated with agitation in Alzheimer disease. Ann Neurol. 2001;49(3):355–61. [PubMed: 11261510]

42. Rosenberg PB, Nowrangi MA, Lyketsos CG. Neuropsychiatric symptoms in Alzheimer's disease: What might be associated brain circuits? Mol Aspects Med. 2015;43–44:25–37.

43. Rapp MA, Schnaider-Beeri M, Grossman HT, Sano M, Perl DP, Purohit DP, et al. Increased hippocampal plaques and tangles in patients with Alzheimer disease with a lifetime history of major depression. Arch Gen Psychiatry. 2006;63(2):161–7. [PubMed: 16461859]

44. Rapp MA, Schnaider-Beeri M, Purohit DP, Perl DP, Haroutunian V, Sano M. Increased neurofibrillary tangles in patients with Alzheimer disease with comorbid depression. Am J Geriatr Psychiatry. 2008;16(2):168–74. [PubMed: 18239198]

45. Ehrenberg AJ, Nguy AK, Theofilas P, Dunlop S, Suemoto CK, Di Lorenzo Alho AT, et al. Quantifying the accretion of hyperphosphorylated tau in the locus coeruleus and dorsal raphe nucleus: the pathological building blocks of early Alzheimer's disease. Neuropathol Appl Neurobiol. 2017;43(5):393–408. [PubMed: 28117917]

46. Gatchel JR, Donovan NJ, Locascio JJ, Schultz AP, Becker JA, Chhatwal J, et al. Depressive Symptoms and Tau Accumulation in the Inferior Temporal Lobe and Entorhinal Cortex in Cognitively Normal Older Adults: A Pilot Study. J Alzheimers Dis. 2017;59(3):975–85. [PubMed: 28697559]

47. Kumar A, Kepe V, Barrio JR, Siddarth P, Manoukian V, Elderkin-Thompson V, et al. Protein binding in patients with late-life depression. Arch Gen Psychiatry. 2011;68(11):1143–50. [PubMed: 22065530]

48. Chen Y, Dang M, Zhang Z. Brain mechanisms underlying neuropsychiatric symptoms in Alzheimer's disease: a systematic review of symptom-general and -specific lesion patterns. Mol Neurodegener. 2021;16(1):38. [PubMed: 34099005]

49. Nobis L, Husain M. Apathy in Alzheimer's disease. Curr Opin Behav Sci. 2018;22:7–13. [PubMed: 30123816]

50. Marshall GA, Fairbanks LA, Tekin S, Vinters HV, Cummings JL. Neuropathologic correlates of apathy in Alzheimer's disease. Dement Geriatr Cogn Disord. 2006;21(3):144–7. [PubMed: 16391476]

51. Vergallo A, Giampietri L, Pagni C, Giorgi FS, Nicoletti V, Miccoli M, et al. Association Between CSF Beta-Amyloid and Apathy in Early-Stage Alzheimer Disease. J Geriatr Psychiatry Neurol. 2019;32(3):164–9. [PubMed: 30913958]

52. Anor CJ, O'Connor S, Saund A, Tang-Wai DF, Keren R, Tartaglia MC. Neuropsychiatric Symptoms in Alzheimer Disease, Vascular Dementia, and Mixed Dementia. Neurodegener Dis. 2017;17(4–5):127–34. [PubMed: 28245482]

53. Attems J, Toledo JB, Walker L, Gelpi E, Gentleman S, Halliday G, et al. Neuropathological consensus criteria for the evaluation of Lewy pathology in post-mortem brains: a multi-centre study. Acta Neuropathol. 2021;141(2):159–72. [PubMed: 33399945]

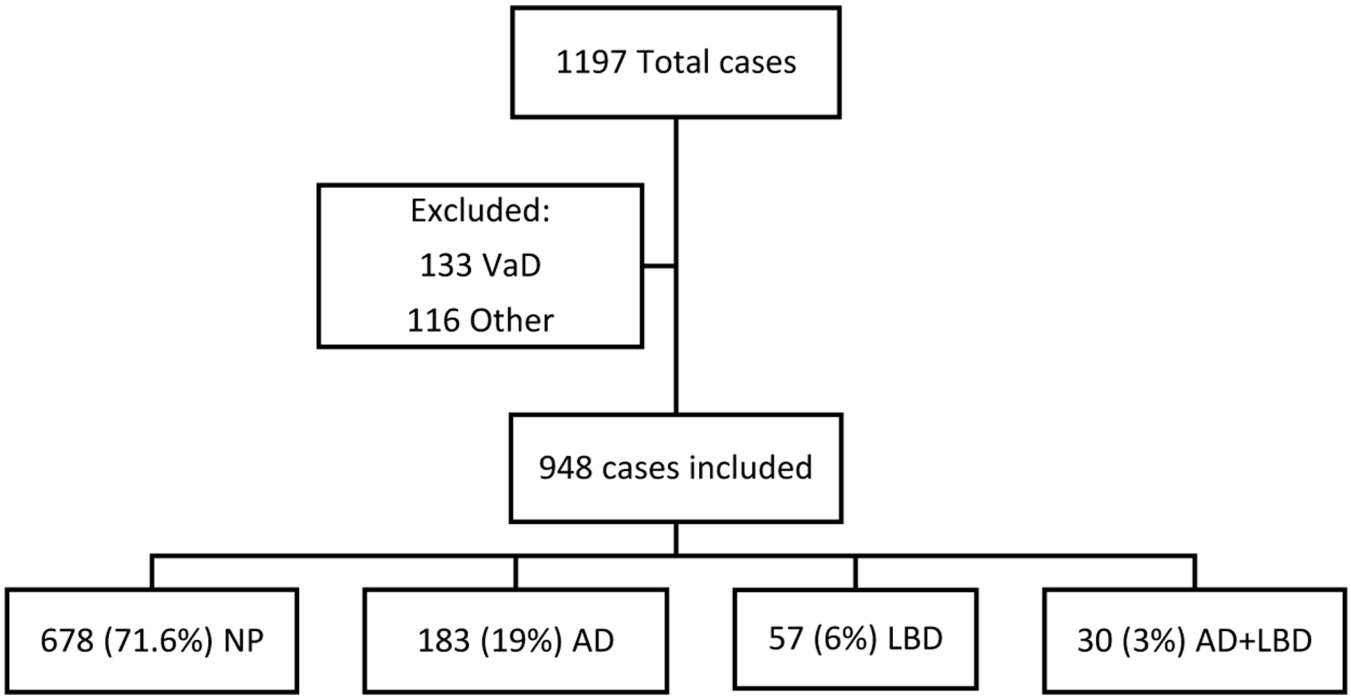

Figure 1.
Flow diagram of included cases classified by neuropathological diagnosis. VaD: vascular dementia; NP: insufficient neuropathology to meet disease classification; AD: Alzheimer's Disease; LBD: Lewy body disease; AD+LBD: met criteria for AD and LBD.

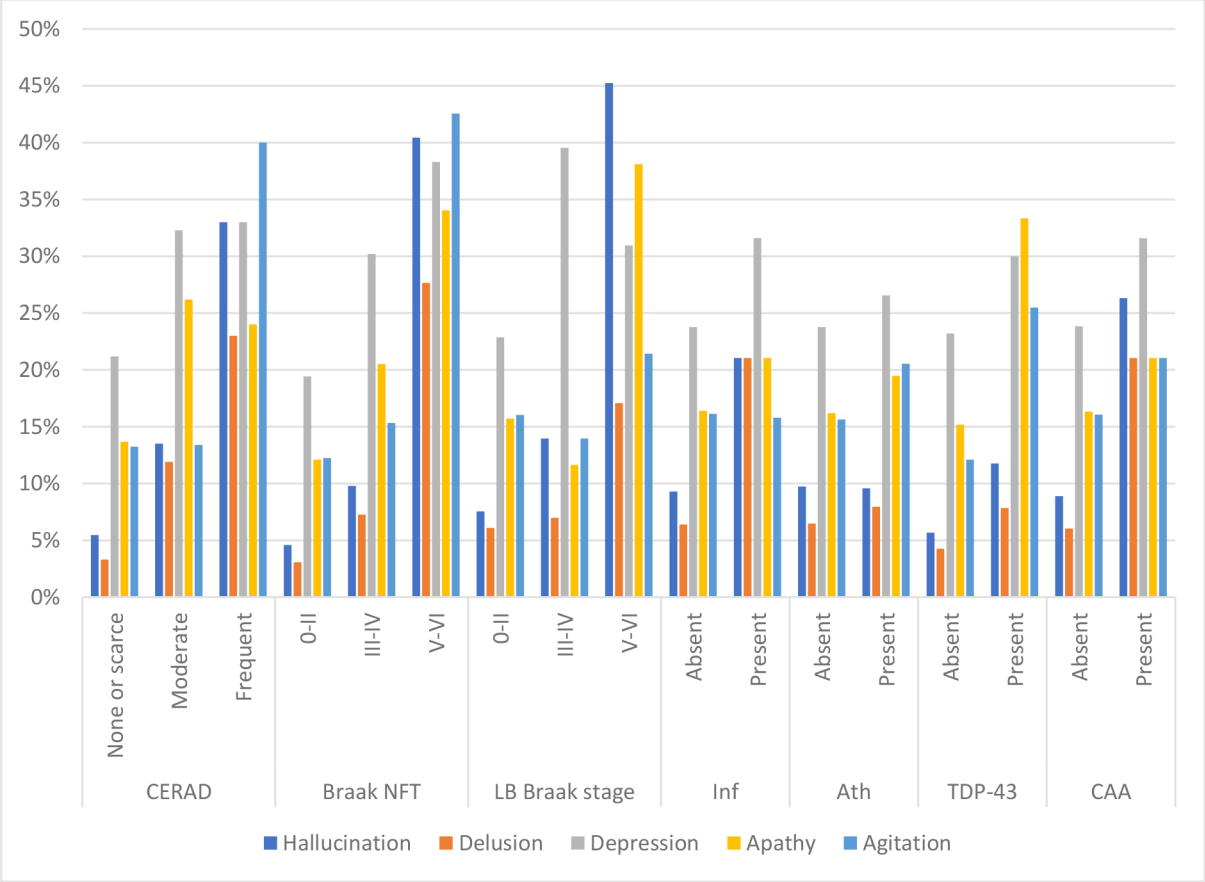

Figure 2.

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

Table 1.

Sociodemographics and cognitive status according to diagnosis made from neuropathological findings irrespective of clinical status (n = 948).

	NP (n=678)	AD (n=183)	LBD (n=57)	AD+LBD (n=30)	*p* value
Age at death (SD)	69.8 (12.1)	81.3 (8.61)	78.8 (7.67)	81.4 (7.66)	<0.001 §
Female n (%)	292 (43.9)	115 (64.6)	23 (40.4)	21 (72.4)	<0.001 †
Education (yrs)	5.09 (4.12)	3.17 (3.00)	3.74 (2.30)	4.51 (3.97)	<0.001 §
Ethnicity					0.014 *
White	454 (68.6)	128 (72.3)	43 (75.4)	15 (51.7)	
Black	73 (11.0)	25 (14.1)	1 (1.75)	7 (24.1)	
Mixed	120 (18.1)	22 (12.4)	10 (17.5)	7 (24.1)	
Other	15 (2.27)	2 (1.13)	3 (5.26)	0	
Dementia, n (%)					<0.001 *
CDR = 0	609 (91.7)	74 (42.1)	35 (61.4)	6 (20.7)	
CDR = 0.5	24 (3.61)	20 (11.4)	8 (14.04)	2 (6.9)	
CDR ≥ 1	31 (4.68)	82 (46.6)	14 (24.6)	21 (72.4)	
Total NPI score (SD)	7.47 (12.18)	16.8 (20.4)	11.5 (13.1)	20.8 (18.5)	<0.001 §

† Chi square test used to determine p value.

* Fisher's exact test used where cells ≤5 participants.

§ One way ANOVA used to determine p value.

NP= no neuropathological diagnosis, AD = Alzheimer's Disease, LBD = Lewy Body disease, AD+LBD = meets classification for AD and LBD.

Table 2.

Neuropsychiatric symptoms stratified by neuropathological diagnostic classification (n=948).

	NP (n=678)	AD (n=183)	LBD (n=57)	AD+LBD (n=30)	p
Hallucinations, n (%)	*28 (4.2)*	*35 (20)*	*10 (17.5)*	*15 (51.7)*	<0.001
NPI mean score (SD)	0.15 (0.96)	*1.31 (3.13)*	*0.84 (2.34)*	*2.59 (3.32)*	
Delusions n, (%)	20 (3)	31 (17.7)	5 (8.9)	5 (17.2)	<0.001*
NPI mean score (SD)	0.16 (1.15)	*1.18 (2.98)*	*0.51 (2.14)*	*0.93 (2.36)*	
Depression n, (%)	134 (20)	57 (32.4)	20 (35.1)	10 (34.5)	0.001
NPI mean score (SD)	1.18 (2.82)	*1.89 (3.29)*	*1.86 (2.84)*	*1.86 (3.42)*	
Agitation n, (%)	87 (13.2)	47 (26.7)	7 (12.3)	8 (27.6)	<0.001
NPI mean score (SD)	0.64 (1.99)	*1.79 (3.51)*	*0.72 (2.14)*	1.69 (3.09)	
Apathy n, (%)	88 (13.4)	43 (24.6)	11 (19.3)	10 (34.5)	<0.001
NPI mean score (SD)	0.65 (2.04)	*1.48 (3.14)*	*1.23 (2.90)*	*2.83 (4.42)*	
Total NPI score (SD)	7.47 (12.18)	*16.8 (20.4)*	*11.5 (13.1)*	20.8 (18.5)	<0.001§
Mean number of symptoms in NPI (SD)	1.43 (1.86)	2.72 (2.56)	2.07 (2.17)	3.33 (2.56)	<0.001§

Chi square test used unless otherwise stated.

*Fisher's exact test used where cell counts ≤5.

§Kruskal Wallis used to determine p value.

NP= no neuropathological diagnosis, AD = Alzheimer's Disease, LBD = Lewy Body disease, AD+LBD = meets classification for AD and LBD.

Table 3.

Association between neuropathological diagnoses and neuropsychiatric symptoms (n=948).

Symptom	Neuropathological diagnostic classification	RRR (95% CI)	p value
Hallucination	NP	1 (reference)	
	AD	4.70 [2.60–8.51]	**<0.001**
	LBD	4.38 [1.95–9.84]	**<0.001**
	AD + LBD	19.3 [8.00–46.3]	**<0.001**
Agitation	NP	1 (reference)	
	AD	2.76 [1.74–4.39]	**<0.001**
	LBD	1.11 [0.48–2.59]	0.80
	AD + LBD	2.79 [1.15–6.79]	**0.02**
Depression	NP	1 (reference)	
	AD	1.72 [1.14–2.58]	**0.009**
	LBD	2.12 [1.16–3.85]	**0.01**
	AD + LBD	1.70 [0.75–3.86]	0.20
Delusion	NP	1 (reference)	
	AD	6.56 [3.34–12.9]	**<0.001**
	LBD	3.22 [1.11–9.27]	**0.03**
	AD + LBD	5.24 [1.71–16.1]	**0.004**
Apathy	NP	1 (reference)	
	AD	1.67 [1.06–2.63]	**0.03**
	LBD	1.36 [0.67–2.79]	0.40
	AD + LBD	2.51 [1.08–5.81]	**0.03**
Total NPI score	NP	1 (reference)	
	AD	1.04 [1.03–1.05]	**<0.001**
	LBD	1.03 [1.01–1.04]	**0.008**
	AD + LBD	1.04 [1.02–1.06]	**<0.001**
Number of Symptoms in NPI	NP	1 (reference)	
	AD	1.31 [1.20–1.42]	**<0.001**
	LBD	1.17 [1.03–1.33]	**0.019**
	AD + LBD	1.43 [1.23–1.65]	**<0.001**

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, and years of education.

Table 4.

Association between neuropathological lesions and neuropsychiatric symptoms (n=948).

Symptom	Neuropathological variable	OR [95% CI]	p value
Hallucinations	Lewy body disease (Braak stage)	**1.30 [1.13–1.49]**	**< 0.001**
	Braak NFT stage	1.24 [0.95–1.62]	0.12
	CERAD neuritic plaque score	0.96 [0.67–1.37]	0.81
	Lacunar infarct	2.95 [0.71– 12.2]	0.14
	Cerebral amyloid angiopathy	1.71 [0.61– 4.73]	0.30
	Hyaline atherosclerosis	1.03 [0.46–2.31]	0.94
	TDP-43 proteinopathy *	0.76 [0.22–2.66]	0.68
Agitation	Lewy body disease (Braak stage)	0.90 [0.78–1.04]	0.17
	Braak NFT stage	**1.30 [1.07–1.57]**	**0.009**
	CERAD neuritic plaque score	0.87 [0.66–1.16]	0.35
	Lacunar infarct	0.80 [0.19–3.29]	0.76
	Cerebral amyloid angiopathy	0.75 [0.29–1.96]	0.56
	Hyaline atherosclerosis	1.56 [0.89–2.74]	0.12
	TDP-43 proteinopathy *	1.18 [0.48–2.91]	0.72
Delusions	Lewy body disease (Braak stage)	0.98 [0.83–1.16]	0.85
	Braak NFT stage	1.17 [0.86–1.58]	0.31
	CERAD neuritic plaque score	1.10 [0.73–1.64]	0.65
	Lacunar infarct	**4.68 [1.12–19.5]**	**0.03**
	Cerebral amyloid angiopathy	2.09 [0.74–5.86]	0.16
	Hyaline atherosclerosis	1.20 [0.50–2.90]	0.68
	TDP-43 proteinopathy *	0.57 [0.13–2.52]	0.46
Depression	Lewy body disease (Braak stage)	1.06 [0.94–1.18]	0.34
	Braak NFT stage	**1.28 [1.09–1.50]**	**< 0.001**
	CERAD neuritic plaque score	0.83 [0.66–1.04]	0.11
	Lacunar infarct	1.37 [0.48–3.90]	0.56
	Cerebral amyloid angiopathy	0.98 [0.44–2.15]	0.96
	Hyaline atherosclerosis	1.17 [0.72–1.89]	0.52
	TDP-43 proteinopathy *	0.90 [0.42–1.94]	0.79
Apathy	Lewy body disease (Braak stage)	0.99 [0.87–1.12]	0.18
	Braak NFT stage	1.14 [0.94–1.39]	0.89
	CERAD neuritic plaque score	**0.70 [0.52–0.93]**	**0.01**
	Lacunar infarct	1.32 [0.30–4.47]	0.66
	Cerebral amyloid angiopathy	0.83 [0.31–2.21]	0.72
	Hyaline atherosclerosis	1.23 [0.70–2.15]	0.48
	TDP-43 proteinopathy *	2.03 [1.00–4.14]	0.05

Symptom	Neuropathological variable	OR [95% CI]	p value
Total score on NPI[#]	Lewy body disease (Braak stage)	1.00 [0.96–1.05]	0.83
	Braak NFT stage	**1.15 [1.05–1.27]**	**0.004**
	CERAD neuritic plaque score	0.91 [0.80–1.03]	0.13
	Lacunar infarct	1.21 [0.87–1.68]	0.26
	Cerebral amyloid angiopathy	1.12 [0.74–1.69]	0.60
	Hyaline atherosclerosis	1.14 [0.90–1.44]	0.27
	TDP-43 proteinopathy [*]	1.23 [0.81–1.87]	0.32

Multivariable logistic regression for neuropsychiatric symptoms by neuropathological substrate. Models adjusted for age, sex, ethnicity, years of education and CDR. NFT: neurofibrillary tangle, CERAD: Consortium to Establish a Reference for Alzheimer's Disease, OR: odds ratio, CI: confidence interval.

[*] n=474.

[#] Multivariable Poisson regression for total score on NPI by neuropathological substrate with IRR: incidence rate ratio.