Mixed Neuropathology and Associations with Cognitive Impairment in Autopsied Older Adults

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Abstract

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Epidemiology

Background: Dementia represents a heterogeneous group of clinical syndromes most often driven by multiple coexisting neuropathologic processes. Although Alzheimer's disease neuropathologic change (ADNC) remains the most recognized contributor, other neurodegenerative and vascular pathologies, including limbic-predominant age-related TDP-43 encephalopathy neuropathologic change (LATE-NC), Lewy body disease (LBD), hippocampal sclerosis, and cerebrovascular lesions, are common and substantially influence cognitive outcomes. Understanding how these mixed pathologies cluster together and contribute to resilience or resistance to cognitive impairment is essential for refining diagnostic frameworks and developing targeted interventions. This dissertation aimed to characterize the heterogeneity of neuropathologic disease and its relationship to clinical outcomes through three complementary aims: (1) to identify biologically coherent clusters of mixed neuropathologic profiles using unsupervised clustering methods; (2) to determine how non-Alzheimer's pathologies

contribute to resistance and resilience to ADNC; and (3) to investigate neuropathologic correlates of resilience to LATE-NC across multiple autopsy cohorts.

Methods: Chapter 2 applies unsupervised hierarchical clustering to 2,899 autopsied National Alzheimer's Coordinating Center (NACC) participants using fourteen neuropathologic features. Chapter 3 examines non-AD pathologies among NACC participants classified as resistant (no/low ADNC, cognitively normal), resilient (intermediate/high ADNC, cognitively normal), or impaired (intermediate/high ADNC, cognitively impaired), using multivariable logistic regression and longitudinal cognitive assessments. Chapter 4 examines factors associated with resilience to advanced LATE-NC (stage 2–3) in both NACC and Adult Changes in Thought (ACT) study participants aged ≥75 years, using regression models stratified by age and longitudinal cognitive analyses in ACT.

Results: Across Chapters 2–4, mixed neuropathologic disease strongly influenced cognitive outcomes. In Chapter 2, five distinct clusters of neuropathologic disease were identified, reflecting common combinations of ADNC, LATE-NC, LBD, TDP-43, and vascular pathology. These clusters were biologically interpretable and often aligned with traditional clinical diagnoses. In Chapter 3, both resistance and resilience to ADNC were associated with markedly lower burden of non-AD pathologies, particularly LBD, LATE-NC, hippocampal sclerosis, and arteriosclerosis. In Chapter 4, resilience to LATE-NC was linked to reduced ADNC and absence of hippocampal sclerosis. Across analyses, lower mixed pathologic burden was strongly associated with cognitive resilience.

Conclusions: Across studies, cognitive outcomes depended on the cumulative and interactive effects of multiple neuropathologic processes. These findings highlight the limitations of single-pathology diagnostic frameworks and support development of biologically grounded subtyping that accounts for mixed pathology. Such approaches will be critical for improving diagnostic precision, understanding mechanisms of resilience, and guiding biomarker and therapeutic development.

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CHAPTER 1. INTRODUCTION

Dementia affects millions of older adults in the United States and represents one of the leading causes of disability and death worldwide.[1] While Alzheimer's disease is the most recognized cause of dementia, most older adults exhibit multiple types of neuropathologic disease at autopsy[1]. These coexisting or "mixed" pathologies, including Alzheimer's disease neuropathologic change (ADNC), Lewy body disease (LBD), limbic-predominant age-related TDP-43 encephalopathy neuropathologic change (LATE-NC), hippocampal sclerosis, and cerebrovascular lesions, collectively shape cognitive trajectories and clinical manifestations. The frequent coexistence of these processes complicates clinical diagnosis and challenges traditional disease categories that assume a single dominant etiology.

Historically, dementia research has emphasized single-disease models, particularly amyloid-β plaques and neurofibrillary tau tangles as the defining features of Alzheimer's disease. However, mounting evidence demonstrates that non-AD pathologies frequently co-occur with ADNC and may independently or synergistically drive cognitive impairment.[2–6] Individuals with similar ADNC burden can have vastly different clinical outcomes, suggesting that additional factors (including co-pathologies, neurobiological resilience mechanisms, and vascular contributions) affect the expression of dementia symptoms.[7–9] Consequently, new frameworks are needed to classify and interpret dementia based on the full spectrum of underlying neuropathologic disease rather than clinical phenotype alone.

The overarching goal of this dissertation was to advance understanding of how mixed neuropathologic disease shapes cognitive outcomes using data-driven classification and resistance and resilience models. Using large, well-characterized autopsy datasets from the National Alzheimer's Coordinating Center (NACC)[10] and the Adult Changes in Thought (ACT) study,[11] this work sought to:

1. Identify distinct combinations of neuropathologic features that represent biologically coherent subtypes of dementia (Chapter 2).
2. Evaluate the role of non-Alzheimer's pathologies in resistance (absence of ADNC) and resilience (normal cognition despite ADNC) (Chapter 3).
3. Determine neuropathologic correlates of resilience to LATE-NC, a common but underrecognized contributor to dementia (Chapter 4).

Together, these aims address critical gaps in understanding the complexity of late-life neurodegenerative disease. In Chapter 2, we apply unsupervised clustering to empirically derive subtypes of neuropathologic disease, moving beyond clinical labels to reveal biological groupings. In Chapter 3, we explore how coexisting pathologies influence who remains cognitively intact despite ADNC, providing insight into mechanisms of resilience. In Chapter 4, we extend this framework to LATE-NC, highlighting parallels and distinctions in resilience mechanisms across pathologies. By integrating these complementary perspectives, this dissertation provides a cohesive, biologically grounded approach to characterizing mixed pathology and its clinical significance.

Ultimately, this research aims to inform a shift from clinically defined syndromes to biologically defined subtypes of dementia. Such an approach could improve diagnostic precision and enhance clinical trial design by accounting for the substantial heterogeneity in neuropathologic burden among individuals with and without dementia. As in vivo biomarkers for amyloid, tau, α-synuclein, and TDP-43 become more widely available, biologically informed subtyping based on the principles demonstrated here will be essential for translating autopsy findings into living patient care. Chapter 5 includes a discussion of overall findings and implications for future research.

CHAPTER 2. UNSUPERVISED CLUSTERING ANALYSIS OF NEUROPATHOLOGIC FEATURES

2.1 ABSTRACT

Background: Dementia is commonly driven by multiple coexisting neuropathologies, complicating diagnosis and treatment. While most research focuses on single pathologies, a data-driven classification of mixed pathologic profiles may better reflect the biological complexity of dementia. This study aimed to identify distinct clusters of neuropathologic disease using autopsy data and evaluate their association with clinical characteristics and diagnoses.

Methods: We conducted an unsupervised hierarchical cluster analysis of 2,899 decedents from the National Alzheimer's Coordinating Center (NACC) with comprehensive neuropathologic assessment within one year of a clinical assessment. Fourteen neuropathologic features, including Alzheimer's disease neuropathologic change (ADNC), cerebrovascular pathology, α-synuclein, TDP-43 inclusions, and hippocampal sclerosis, were used to derive clusters. We compared neuropathologic, demographic, and clinical features of the resulting clusters.

Results: Five distinct neuropathologic clusters were identified: (1) *TDP-43/HS* (TDP-43 inclusions and hippocampal sclerosis, younger age); (2) *Mild* (low pathology burden with higher FTD-tau); (3) *ADNC + LATE/HS* (older age, high LATE-NC and hippocampal

sclerosis); (4) *ADNC + LBD*; and (5) *ADNC* (classic Alzheimer's pathology). Vascular pathologies were prevalent across all clusters, and mixed pathologies were highly prevalent (85% of participants had ≥5 pathologies). Pathology in each cluster generally corresponded to the primary clinical diagnosis for those who were cognitively impaired, but there was variability. For example, over 20% of those in the *TDP-43/HS* cluster were clinically diagnosed with Alzheimer's disease, despite minimal ADNC. Clusters also differed in cognitive outcomes, motor and behavioral symptoms, and age at onset and death.

Conclusions: Despite the diverse combinations of pathologies present at autopsy, unsupervised cluster analysis revealed biologically distinct subtypes of neuropathologic disease, often aligned with clinical diagnoses. These results support the use of data-driven, pathology-based classification to improve research precision and inform future clinical strategies. As the availability of in vivo biomarkers expands, biologically defined subtypes may enhance disease treatment and clinical trial design.

2.2 INTRODUCTION

An estimated 11% of people over age 65 in the United States have some form of dementia.[12] While Alzheimer's disease remains the most recognized cause of dementia, most individuals have multiple types of neuropathologic disease independently associated with cognitive impairment.[2–4,6,13–15] This multiple etiology or mixed pathologies dementia is highly prevalent in aging populations and complicates both diagnosis and treatment.[16] Older adults with multiple types of neuropathologic disease

are at higher risk for cognitive impairment.[17–20]

Conducting research with the lens of multiple disease pathologies may allow more targeted and effective therapeutic treatments. A wide array of neuropathologic features are associated with dementia, including beta-amyloid plaques,[21,22] neurofibrillary tau tangles,[23] cerebral infarcts,[24] Lewy bodies[25], and transactive response DNA-binding protein 43 (TDP-43).[26,27] Despite the known co-occurrence of these pathologies, the majority of existing studies concentrate on one or two neuropathologic features at a time, limiting our ability to capture the heterogeneity of the aging brain. Numerous studies attempt to classify subtypes of a single clinical disease[28], but given the extensive possible combinations of neuropathologic disease that are common at autopsy, a classification system is needed that incorporates a wide range of neuropathologic disease to define profiles of neuropathologic dementia that are most similar.

Many studies have performed classification based on imaging results such as cortical thickness or gray matter volume.[29–32] While valuable, these methods often infer underlying pathology indirectly and may not fully capture the complex neuropathological landscape seen at autopsy. We have found only one prior study that has attempted to classify subjects by their mixed pathologic profiles using cluster analysis.[33] However, that study did not compare the resulting clusters to existing etiologic diagnoses, missing a critical opportunity to validate whether data-driven subtypes align with or challenge traditional diagnostic categories.

Classifying individuals based on underlying neuropathologic features, rather than relying on clinical diagnoses that can be subjective and influenced by various biases, may offer a more accurate and biologically grounded understanding of dementia. Clinical diagnoses often rely on behavioral symptoms, patient history, and limited biomarker data, which may not fully reflect the underlying disease processes.[34,35] Consequently, misdiagnosis or oversimplification of complex cases is common. By identifying distinct neuropathologic clusters based on actual neuoropathology findings, researchers may uncover novel subtypes of dementia that better reflect disease biology and progression.

In the present study, we applied unsupervised cluster analysis to autopsy-derived neuropathologic data from nearly 3,000 participants in the National Alzheimer's Coordinating Center (NACC) database. NACC serves as the centralized repository for standardized clinical and pathological data collected from 46 Alzheimer's Disease Research Centers (ADRCs) across the United States. Using this large dataset, we sought to identify distinct clusters of individuals based on combinations of key neuropathologic features, including Alzheimer's pathology, cerebrovascular disease, Lewy bodies, and TDP-43 inclusions. We then examined how these clusters differed with respect to demographic and clinical characteristics, including primary clinical diagnosis. Our goal was to determine whether meaningful and biologically coherent profiles of neuropathologic dementia could be identified and whether these profiles align with or challenge current conceptions of disease subtypes.

2.3 METHODS

Data Collection

NACC has data on over 54,000 participants collected since 2005. Data are collected by clinicians or trained interviewers at the ADRCs using standardized forms and maintained by NACC as the Uniform Data Set (UDS).[36–38] Longitudinal clinical data are collected from participants and their co-participants (usually a spouse or child) at approximately annual follow-up visits as long as the subject is able. Late-stage subjects who become unable to participate may be followed for autopsy after they discontinue their UDS follow-up visits. Participants have an average of 3.7 visits completed, with two-thirds of participants returning for at least one follow-up visit after their initial visit. Participants with a range of cognitive statuses (normal to demented) and diagnoses are included, with 37% of participants having normal cognition at their most recent visit. Clinical diagnoses and assessments of cognitive status are made by a clinician or a consensus team at the ADRCs. Participants come to the ADRCs from a variety of sources according to each ADRC's protocols, including clinician referral, self-referral, active recruitment through community organizations, and volunteers wanting to contribute to dementia research. The NACC data's comprehensive inclusion of over 1,000 variables collected via standardized forms and instructions makes it ideal for this and many other studies of dementia etiology.[39]

Nearly 60% of deceased participants consented to brain autopsy and are included in the neuropathology dataset, which includes standardized data on neuropathologic evaluations performed at the ADRCs according to their own protocols.[40] The NACC

neuropathology database was designed by ADRC Neuropathology Core leaders, first implemented in 2002, and has undergone several revisions since to reflect research developments.[40] The dataset contains over 8,000 autopsies, 62% (5,231) of which were completed using a neuropathology form that included assessment of TDP-43.

Written informed consent was obtained from all participants and their study co-participants; institutional review board (IRB) approval was obtained from all individual ADRCs. Research using the NACC database was approved by the University of Washington IRB.

Study Population

The study sample was extracted from the March 2025 data freeze of the NACC database. We limited the data to participants in the NACC database with a version 10 or later neuropathology form, since information on TDP-43 was not collected prior to that version. To reduce misclassification of cognitive status at death, participants must have either had their last UDS visit within one year of autopsy, or been diagnosed with dementia at any point prior to autopsy (since reversions from dementia are rare). Including participants with dementia but no recent UDS visit also reduces potential selection bias if only participants who were unimpaired enough to complete UDS visits were included. To increase precision, we excluded participants with rare pathologies (Down syndrome, pigment-spheroid degeneration/neurodegeneration with brain iron accumulation (NBIA), multiple system atrophy, trinucleotide repeat disease), malformation of cortical development, metabolic/storage disorder of any type, white

matter disease (leukodystrophy, multiple sclerosis or other demyelinating disease), contusion/traumatic brain injury of any type (acute or chronic), neoplasm (primary or metastatic), infectious process of any type (encephalitis, abscess, etc.), herniation (any site), Prion disease, ALS/motor neuron disease (MND), cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL).

Analysis

Cluster analysis is a type of classification analysis that maximizes similarities between subjects in the cluster and minimizes similarities with other clusters.[41] Hierarchical clustering techniques were used for this analysis, since the optimal number of classes was unknown in advance.[42] Hierarchical clustering can be used with categorical, continuous, and ordinal variables; the only requirement is to have a pairwise distance between each pair of observations. There are several methods to computing distance between observations, although hierarchical clustering is not as sensitive to the distance method chosen as other techniques. For this analysis, we ran a single linkage hierarchical clustering analysis using Ward's linkage method, which calculates distance between points using Gower's distance and can accommodate non-continuous data.[42] Values for ordinal and continuous variables were scaled to a minimum of zero and maximum of one to ensure variables are not given unequal weight in the cluster analysis.

Unsupervised hierarchical clustering algorithms start by putting each data point into its own cluster. Then, the distance between each cluster is calculated and the two clusters

with the smallest distance are combined into one cluster, resulting in one fewer cluster. This is repeated until all the data points are in a single cluster.[42] The results are typically represented in a dendrogram, with each data point shown on the x-axis and the distance between clusters shown on y-axis (height). To determine the optimal number of clusters, we used a combination of internal validation statistics and subjective measures (reviewing the dendrogram and cohesiveness of resulting clusters). We specified a minimum of three clusters and a maximum of 12 clusters using the NbClust package in R, and then reviewed the 30 validation indices provided.[43,44] The minimum number of clusters was set to three to avoid the trivial two-cluster solution of Alzheimer's disease neuropathologic change (ADNC) versus non-ADNC.

Our clustering algorithm included the 14 neuropathologic measures described in **Table 2.1**: amyloid plaques (Thal phase, neuritic plaque density); tau neurofibrillary tangles (Braak stage, frontotemporal lobar degeneration (FTLD) tau presence); vascular pathology (infarcts, microinfarcts, arteriosclerosis, atherosclerosis, cerebral amyloid angiopathy); amygdala-predominant Lewy Body Disease (LBD); level of α-synuclein; transactive response DNA-binding protein 43 (TDP-43) inclusions (FTLD-TDP presence; LATE-NC); and hippocampal sclerosis. Note that we included Thal, CERAD, and Braak scores separately, instead of the NIA-AA ABC score[45], to allow for non-Alzheimer's diseases such as Primary Age-Related Tauopathy (PART).[46]

In addition to descriptions of the neuropathologic profiles defined by the clusters, we compared neuropathologic, demographic, and clinical features of the resulting clusters with t-tests for continuous variables and Pearson's chi-square tests for categorical

variables. Variables included: neuropathologic features, number of neuropathologic features; primary clinical diagnosis at last UDS visit, measured as percentage with each diagnosis; age at death; sex; race; years of education; level of cognitive impairment at last UDS visit, measured by diagnosed cognitive status and global Clinical Dementia Rating (CDR) score,[47] from 0 (normal cognition) to 3 (severely demented); clinical symptoms at last UDS visit, and clinical dementia syndrome at last visit.

All tests were two-sided using $\alpha = 0.05$, adjusted for multiple comparisons using Bonferroni correction[48]. Analyses were conducted using R (version 4.5.1).[49]

2.4 RESULTS

The cluster analysis included 2,899 participants in the NACC database who meet the criteria outlined above (see study flow diagram in **Figure 2.1**). These participants are on average 79 years old at death, highly educated (mean 15.8 years of education), predominately white (91%), and cognitively impaired (89% with dementia at their last UDS visit) (**Table 2.2**). Mixed neuropathologies are common in this population, with 85% having some level of five or more of the 14 neuropathologic measures.

After running the clustering algorithm on the 2,899 participants that met inclusion criteria, we reviewed the dendrogram and validation indices provided by NBClust to determine the appropriate number of clusters. The indices supported a five-cluster solution (**Figure 2.2**). We identified three clusters that were characterized by high levels of ADNC: Cluster 5 (ADNC), Cluster 4 (ADNC + LBD), and Cluster 3 (ADNC +

LATE/HS). Cluster 1 (TDP-43/HS) was characterized by high levels of FTD-TDP, LATE-NC, or hippocampal sclerosis, with relatively mild burden of other pathologies. The remaining Cluster 2 (Mild) exhibited lower burden across neuropathologic domains, except for LBD and FTLD-tau. Cerebrovascular pathologies were prevalent across all clusters. **Figure 2.3** shows a simplified heatmap of the five-cluster solution with mean severity of each neuropathology by cluster, with darker cells indicating higher severity.

The primary etiologic diagnosis at their last visit generally corresponded with the dominant neuropathologies of each cluster (**Figure 2.4**). Alzheimer's disease was by far the most common diagnosis amongst the three ADNC-based clusters, even when co-pathologies like LBD, LATE-NC, or hippocampal sclerosis were present. Cluster 1 with high burden of LATE-NC and FTLD-TDP was primary diagnosed as FTLD, with 68% receiving a diagnosis of PSP, CBD, FTLD with motor neuron disease, or other FTLD subtype. An additional 23% of individuals in this cluster were diagnosed with Alzheimer's disease, likely reflecting symptomatic LATE-NC. (Note that in the version of the UDS used for diagnostic assessment in this study, LATE-NC diagnosis would only be captured as "other"). The primary diagnosis in Cluster 2 (Mild) was the most heterogenous, reflecting the lower and more variable neuropathologic burden in that group.

We next compared neuropathologic, demographic, and clinical features of each cluster against the largest Cluster 5 (ADNC), which served as a reference group (**Table 2.3**)**.**

Cluster 1 (TDP-43/HS) is defined by high burden of FTLD-TDP, LATE-NC, and hippocampal sclerosis. This cluster showed significantly higher prevalence of these pathologies than Cluster 5. Despite marked differences in underlying pathology and etiologic diagnoses, cognitive outcomes (MoCA, MMSE, CDR, cognitive status, and cognitive symptoms) were not significantly different from Cluster 5, except for a lower prevalence of visuospatial function symptom in Cluster 1. Behaviorally, this group had significantly higher rates of apathy, disinhibition, and personality change. Participants were also more likely to experience slowness as a motor symptom in this cluster.

Participants in **Cluster 2 (Mild)** had significantly lower levels of ADNC and other neuropathologies compared to Cluster 5, though they showed significantly higher severity of LBD and prevalence of FTD-tau. Clinically, they had the highest cognitive test scores (MMSE, MoCA) and lowest prevalence of cognitive symptoms across all clusters. They also exhibited the highest frequency of motor symptoms, including gait disorders and falls.

While **Cluster 3 (ADNC + LATE/HS)** also had substantial ADNC, their burden was significantly lower than Cluster 5. They were instead defined by very high levels of LATE-NC and near-universal hippocampal sclerosis, but very low FTLD-TDP burden. Demographically, this cluster had the oldest age at cognitive symptom onset and death among all clusters. Despite distinct pathology, cognitive outcomes and rates of behavioral and motor symptoms were similar to Cluster 5.

Cluster 4 (ADNC + LBD) had similar ADNC levels to Cluster 5 but significantly higher LBD burden. Although Cluster 4 participants were diagnosed with MCI and dementia at similar rates to Cluster 5, they had higher CDR scores (indicating worse cognition). They were more likely to exhibit visuospatial deficits, fluctuating cognition, visual hallucinations, and slowness. Despite mixed pathology, AD remained the most common primary clinical diagnosis in this group.

2.5 DISCUSSION

In this study, we used unsupervised hierarchical clustering to identify neuropathologic profiles in a large sample of nearly 3,000 autopsied participants from the NACC database. Despite the extensive heterogeneity of mixed neuropathologic burden at the individual level, our analysis revealed five distinct and biologically coherent clusters, each characterized by unique combinations of neuropathologic features. Importantly, while clinical diagnoses often aligned with the dominant pathology in each cluster, notable discrepancies were observed, particularly in groups where non-Alzheimer's pathologies played a significant role. These findings highlight the potential of data-driven classification methods to refine our understanding of dementia subtypes and provide a more biologically grounded framework for research and clinical application.

Our cluster analysis confirmed that mixed pathologies are the rule rather than the exception in aging brains. Over 85% of individuals exhibited five or more co-occurring neuropathologic features. Despite this complexity, distinct clusters emerged, including three centered on ADNC: one with isolated ADNC (Cluster 5), one with coexisting Lewy

body pathology (Cluster 4), and one with cooccurring LATE-NC and hippocampal sclerosis (Cluster 3). Cluster 1 was defined by high burden of TDP-43 pathology and hippocampal sclerosis without ADNC, while the final cluster (Cluster 2) demonstrated relatively low levels of all measured pathologies, albeit with a higher prevalence of Lewy bodies and FTLD-tau.

We found that clinical diagnoses generally reflected the predominant pathology of each cluster. For example, ADNC-dominant clusters were most frequently diagnosed as Alzheimer's disease, and the TDP-43 cluster was most often diagnosed with FTLD. However, discrepancies were observed. In Cluster 1, which had high TDP-43 and hippocampal sclerosis burden but low ADNC, over 20% of participants were still diagnosed with Alzheimer's disease, possible reflecting that clinical features of LATE-NC mimic those of AD.[27] Similarly, Cluster 4 participants had mixed ADNC and Lewy body pathology but were only diagnosed with Lewy body dementia syndrome in 19% of cases, potentially under-recognizing the contribution of Lewy body disease to the clinical syndrome.

Clusters showed meaningful differences in demographic and clinical characteristics. For example, Cluster 3 (ADNC + LATE/HS) had the oldest ages of symptom onset and death, supporting prior studies suggesting LATE-NC is predominantly a disease of advanced age.[27] In contrast, Cluster 1 (TDP-43/HS) included younger individuals and showed behavioral symptoms, such as apathy and disinhibition, more typical of FTLD syndromes.[50] Cluster 2, with the mildest neuropathologic burden, showed the lowest

cognitive impairment and lowest frequency of cognitive symptoms, but had a higher prevalence of motor symptoms, consistent with the increased Lewy body pathology in this group.[51]

To our knowledge, only one prior study has used cluster analysis to classify neuropathologic disease across a wide scope of dementia syndromes. In that study, Cornblath et al. (2019) derived six clusters that included tauopathy, ADNC, TDP-43, α-synuclein, mixed ADNC + LBD, and a low-pathology group.[52] Our results are broadly consistent with that work, though our analysis incorporated LATE-NC staging, used a larger national dataset, and importantly, evaluated how data-derived clusters corresponded to clinical diagnoses and cognitive outcomes. Our findings demonstrate that, even in a highly heterogeneous sample, unsupervised clustering yields biologically interpretable groups that often align with diagnostic categories.

Traditional classification schemes for neurodegenerative disease tend to rely heavily on clinical presentation, which can be shaped by numerous factors, including clinician expertise, available diagnostic tools, and patient demographics.[53,54] As a result, clinically defined syndromes may fail to reflect the underlying biology of the disease, especially in cases with substantial co-pathology. Our results suggest that data-driven classification based on neuropathology can reveal patterns that may be overlooked by symptom-based diagnostic frameworks. This shift toward pathological subtyping could ultimately improve the precision of research, diagnosis, and treatment planning.

Using pathologic profiles, rather than clinical diagnoses, as exposure groups in observational studies may reduce misclassification bias and improve estimates of risk factors, progression, and response to interventions. For example, grouping participants based on shared neuropathologic burden may allow researchers to detect more nuanced relationships between exposures (e.g., vascular risk factors) and outcomes (e.g., rate of cognitive decline), compared to grouping by potentially heterogeneous diagnostic categories like Alzheimer's dementia. As in vivo biomarkers for key pathologies (amyloid, tau, TDP-43, α-synuclein) are developed, it may be possible to assign living individuals to pathologic clusters in clinical settings. Progress in this area could allow clinicians to construct patient-specific neuropathologic profiles. Knowing a patient's likely pathologic subtype could inform prognosis and treatment planning.

Our findings may also help refine eligibility criteria for clinical trials. Current trials often target individuals with Alzheimer's disease, but as our results suggest, many such individuals may have substantial co-pathology that could influence treatment response. Classifying patients by mixed pathology subtype, rather than amyloid alone, may lead to more homogeneous study populations, increasing the likelihood of detecting treatment effects. Furthermore, trials could be designed to target common subtypes (e.g., ADNC + LATE-NC) that are not considered by current therapeutic approaches.

Several limitations of this study should be considered. Participants were predominantly white, non-Hispanic, and highly educated, limiting the generalizability of our findings to more diverse populations. Neuropathologic data are based on autopsy and may not

perfectly reflect the participant's pathology at their last clinic visit, and the clinical presentation at the last clinic visit may not accurately reflect that at death. To mitigate this concern, we included only participants whose last clinical visit was within one year of death or who had a dementia diagnosis to improve alignment between clinical status and postmortem pathology. Individuals who consent to brain autopsy may be systematically different from those who do not, potentially introducing selection bias. However, prior studies suggest that the prevalence of neuropathologic features among autopsied participants does not differ substantially from non-autopsied participants when inverse probability weighting is applied, particularly among participants with dementia.[55,56] Additionally, while clustering algorithms allow for the discovery of natural groupings in the data, they rely on several subjective decisions, including choice of distance metric, linkage method, and number of clusters. We attempted to minimize bias by using validated methods, internal validation indices, and biological interpretability to guide these choices.

Our study demonstrates that unsupervised clustering of neuropathologic features can identify biologically coherent subtypes of dementia, which correspond fairly well with current clinical diagnoses. These findings underscore the complexity of neurodegenerative disease and suggest that a biologically informed classification system may improve the accuracy and utility of research and clinical care. This work opens several avenues for future research. Longitudinal studies could explore how these clusters relate to cognitive decline over time or response to treatment. As in vivo biomarkers become more widely available, neuropathologic clusters can be used in

clinical trials. Additionally, researchers could integrate multi-omics data (e.g., genomics, proteomics) to refine cluster definitions further.

2.6 FIGURES AND TABLES

Table 2.1. Neuropathology measures included in cluster analysis

Neuropathology	Measure	Values
Amyloid plaques	Thal phase (A score)[21]	0: Phase 0 1: Phase I 2: Phase II 3: Phase III 4: Phase IV 5: Phase V
	CERAD neuritic plaques score (C score)[57]	0: none 1: sparse 2: moderate 3: frequent
Neurofibrillary tau tangles	Braak stage (B score)[58]	0: Stage 0, not present 1: Stage I 2: Stage II 3: Stage III 4: Stage IV 5: Stage V 6: Stage VI
	presence of FTLD-tau	0: Absent 1: Present
Vascular brain injury	number of gross infarcts in cerebral cortex, subcortical cerebral/periventricular white matter, deep cerebral gray matter, internal capsule, brainstem, or cerebellum	0: 0 1: 1 2: 2 3: 3+
	number of microinfarcts in cerebral cortex, subcortical or periventricular white matter, subcortical gray matter, or brainstem and cerebellum	0: 0 1: 1 2: 2 3: 3+
	severity of cerebral amyloid angiopathy	0: None 1: Mild 2: Moderate 3: Severe
	severity of arteriosclerosis	0: None 1: Mild 2: Moderate 3: Severe
	severity of atherosclerosis	0: None 1: Mild 2: Moderate 3: Severe
Hippocampal sclerosis	presence of hippocampal sclerosis	0: Absent 1: Present
Lewy body pathology	level of α-synuclein	0: None 1: Olfactory bulb 2: Brainstem-predominant 3: Limbic (transitional) 4: Neocortical (diffuse)
	amygdala-predominant LBD[59]	0: Absent 1: Present
TDP-43	LATE-NC stage	0: absent in amygdala

		1: localized to amygdala or localized to hippocampus without amygdala 2: extension to hippocampus 3: extension to the neocortex
	presence of FTLD-TDP	0: Absent 1: Present

Abbreviations: CERAD = Consortium to Establish a Registry for Alzheimer's Disease; FTLD = frontotemporal lobal degeneration; LBD = Lewy Body Disease; TDP-43 = transactive response DNA-binding protein 43; LATE-NC = limbic-predominant age-related TDP-43 encephalopathy neuropathologic change

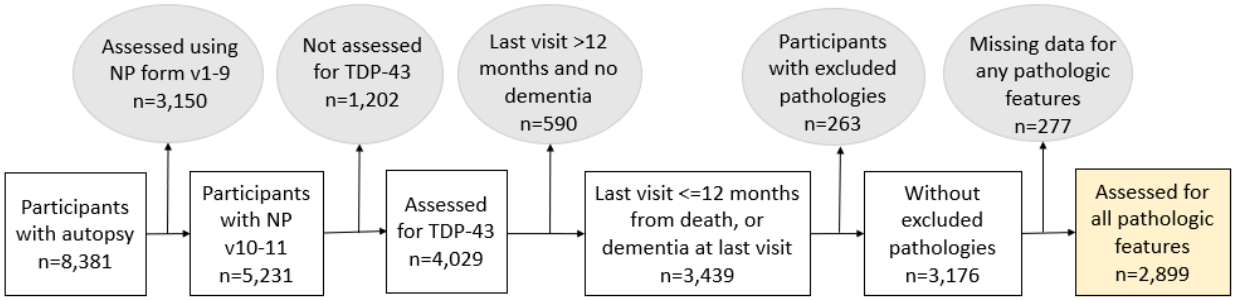

Figure 2.1. Study sample flow diagram. The diagram illustrates inclusion and exclusion criteria used to derive the final sample of 2,899 participants.

Abbreviations: NP=neuropathology; TDP-43 = transactive response DNA-binding protein 43

Table 2.2. Demographic and clinical characteristics of study sample

	mean or n	SD or %
n	2,899	
Demographics		
Age at death (years), mean (SD)	79.5	(11.4)
Non-white, n (%)	252	(8.8%)
Years of education, mean (SD)	15.8	(3.0)
Female (%)	1,400	(48.3%)
# of APOE e4 alleles (%)		
0	1,355	(52.1%)
1+	1,247	(49.0%)
Primary etiologic diagnosis (%)		
AD	1,850	(63.8%)
LBD	172	(5.9%)
FTLD	501	(17.4%)
Vascular dementia	79	(2.7%)
Other	103	(3.4%)
Not cognitively impaired	194	(6.7%)
MoCA at last visit, mean (SD)	13.9	(7.9)
MMSE at last visit, mean (SD)	17.6	(8.9)
Cognitive status (%)		
Cognitively normal	194	(6.7%)
Impaired-not-MCI	22	(0.8%)
MCI	106	(3.7%)
Demented	2,577	(88.9%)
Age cognitive decline began (years), mean (SD)	68.5	(11.7)
CDR global (%)		
0	186	(6.4%)
0.5	339	(11.7%)
1	587	(20.2%)
2	805	(27.8%)
3	982	(33.9%)
Cognitive symptoms		
Memory (%)	2,636	(91.1%)
Orientation (%)	1,622	(83.7%)
Executive function (%)	2,604	(90.2%)
Language (%)	2,091	(72.7%)
Visuospatial function (%)	1,594	(58.3%)
Attention (%)	1,727	(62.2%)
Fluctuating cognition (%)	380	(14.2%)
Behavioral symptoms		
Apathy (%)	1,490	(52.0%)
Depressed mood (%)	878	(31.1%)
Visual hallucinations (%)	376	(13.5%)
Auditory hallucinations (%)	135	(4.9%)
Delusions (%)	475	(17.1%)

Disinhibition (%)	711	(24.8%)
Irritability (%)	936	(32.6%)
Agitation (%)	778	(27.0%)
Personality change (%)	517	(18.1%)
Motor symptoms		
Gait disorder (%)	1,214	(42.7%)
Falls (%)	720	(25.3%)
Tremors (%)	638	(22.5%)
Slowness (%)	1,250	(43.9%)
Clinical Dementia Syndrome		
Amnestic multidomain dementia (%)	1,243	(62.4%)
Posterior cortical atrophy (%)	46	(2.3%)
Primary progressive aphasia (%)	246	(8.5%)
Behavioral variant FTD (%)	271	(9.3%)
Lewy body dementia (%)	211	(7.3%)
Non-amnestic multidomain dementia (%)	56	(2.8%)

Abbreviations: SD=standard deviation; AD=Alzheimer's disease, LBD=Lewy Body Disease; FTLD=frontotemporal lobar degeneration; FTD=frontotemporal dementia; MoCA = Montreal Cognitive Assessment; MMSE = Mini-Mental State Exam; CDR = Clinical Dementia Rating

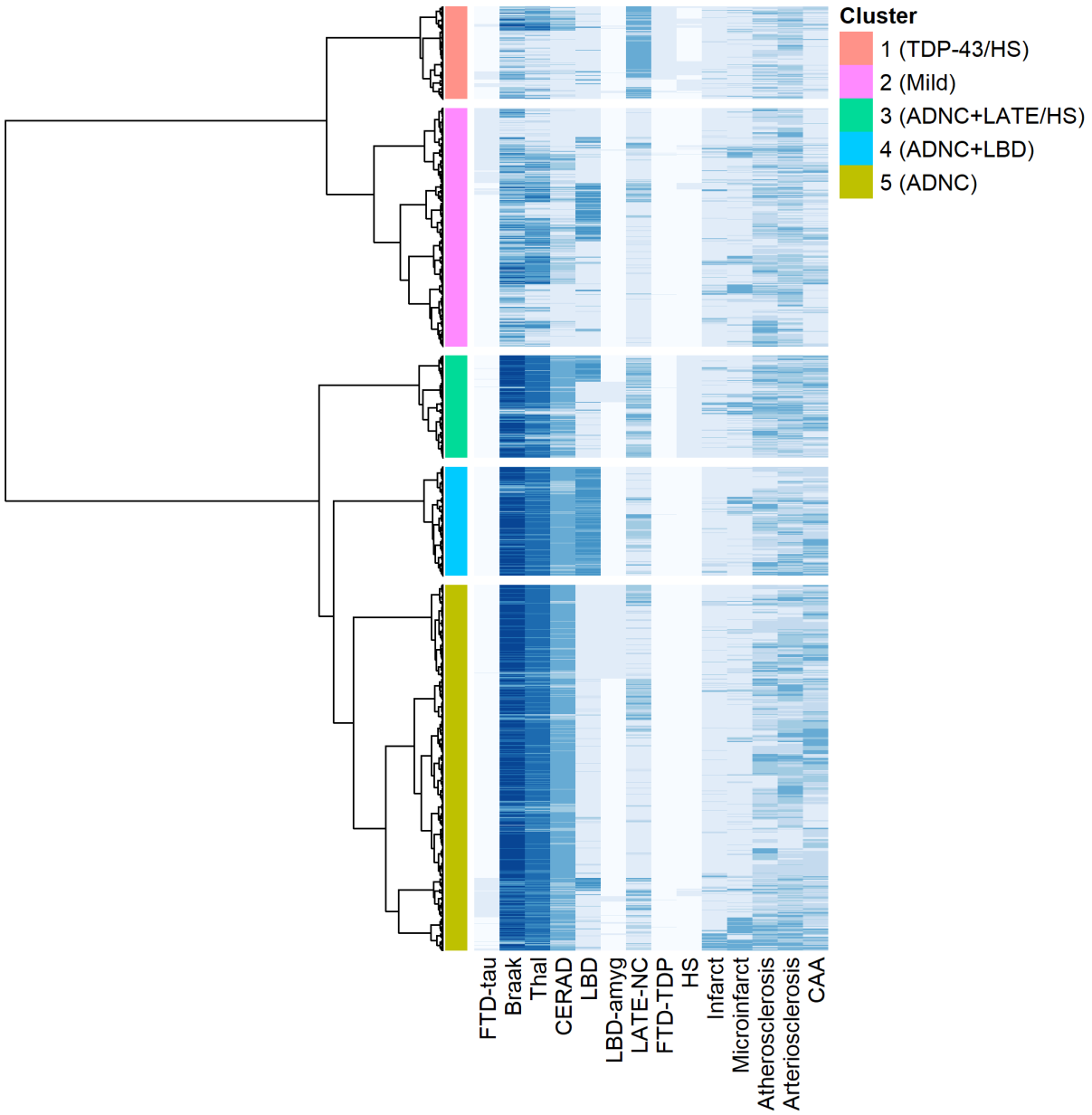

Figure 2.2. Dendrogram and neuropathological feature heatmap of five-cluster solution. Dendrogram (on left) displaying hierarchical agglomerative clustering results of 2,899 autopsied participants based on 14 neuropathologic features. Dendrogram height indicates distance between merged clusters. The optimal five-cluster solution was selected based on internal validation indices and visual inspection. Each cluster is represented by a different color in the dendrogram; from the top: Cluster 1 (TDP-43/HS), Cluster 2 (Mild), Cluster 3 (ADNC+LATE/HS), Cluster 4 (ADNC+LBD), Cluster 5 (ADNC). On the heatmap, each row represents one participant, with darker colors indicating higher severity of neuropathologic disease.

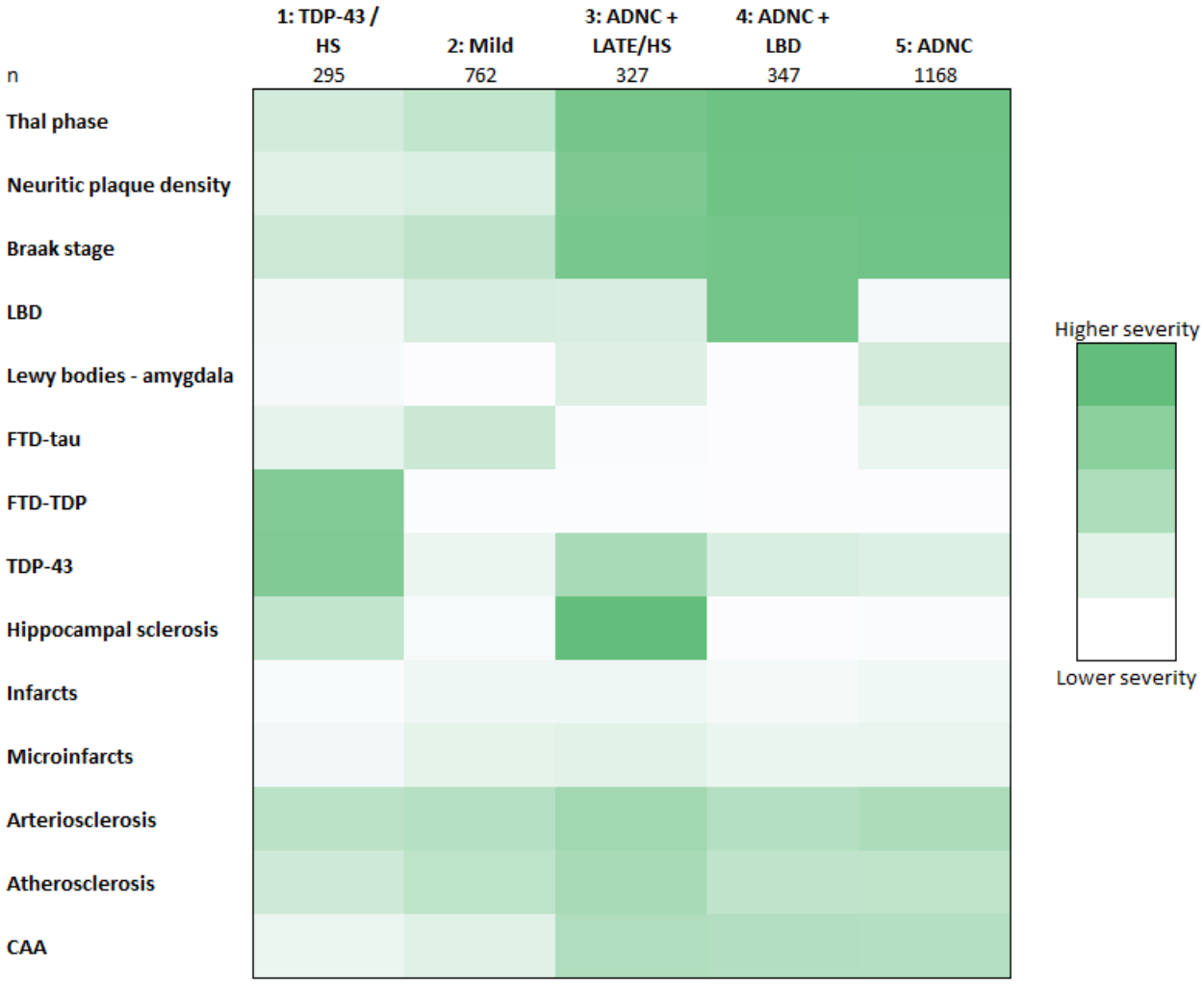

Figure 2.3. Heatmap of neuropathologic severity by cluster. Simplified heatmap displaying mean severity of each scaled neuropathologic feature across the five derived clusters. Darker cells indicate higher mean severity.

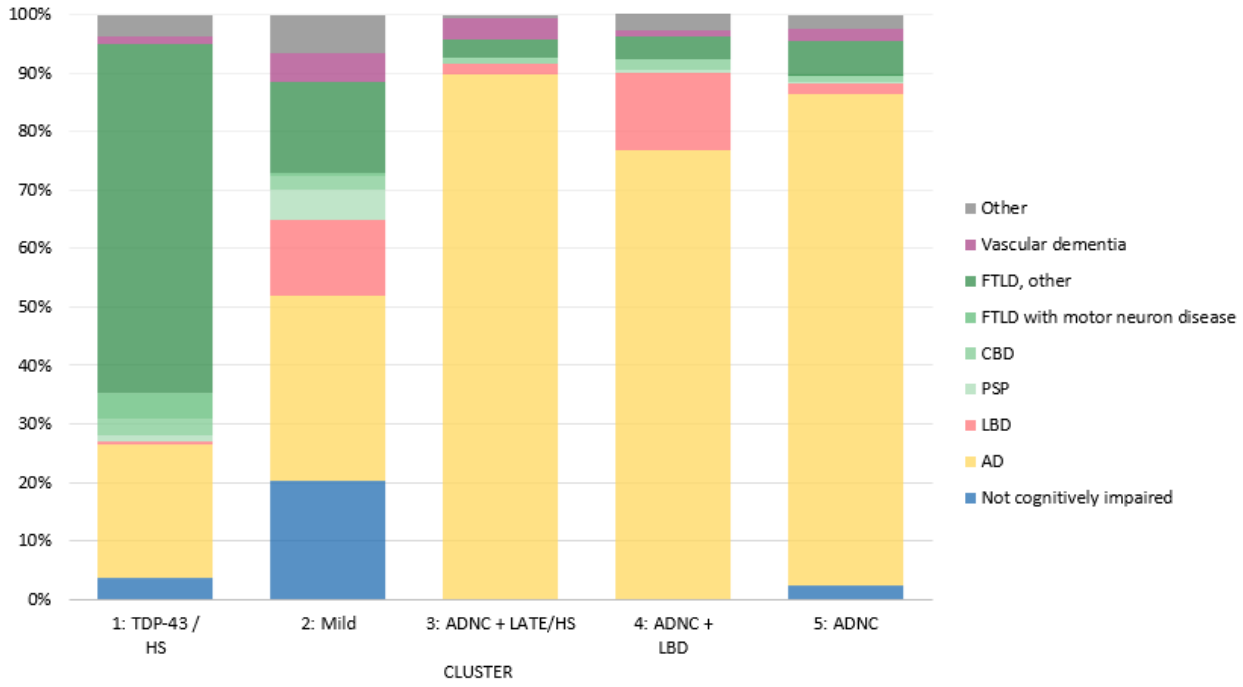

Figure 2.4. Primary etiologic diagnosis at last clinical visit by cluster. Distribution of primary clinical diagnosis at last UDS visit for participants with cognitive impairment, stratified by cluster.

Table 2.3. Neuropathologic, demographic, and clinical characteristics by cluster

	1: TDP-43 / HS			2: Mild			3: ADNC + LATE/HS			4: ADNC + LBD			5: ADNC	
	mean or n	SD or %	p-value	mean or n	SD or %	p-value	mean or n	SD or %	p-value	mean or n	SD or %	p-value	mean or n	SD or %
n	295			762			327			347			1,168	
Neuropathologic features														
Thal phase, mean (SD)	1.4	(1.6)	**<0.0001**	1.9	(1.7)	**<0.0001**	4.4	(1.1)	**<0.0001**	4.7	(0.6)	0.4392	4.7	(0.7)
CERAD score, mean (SD)	0.5	(1.0)	**<0.0001**	0.7	(0.9)	**<0.0001**	2.5	(0.8)	**<0.0001**	2.8	(0.5)	0.3476	2.8	(0.5)
Braak stage, mean (SD)	1.9	(1.7)	**<0.0001**	2.4	(1.5)	**<0.0001**	5.2	(1.3)	**<0.0001**	5.4	(1.0)	0.0836	5.5	(0.9)
LBD, mean (SD)	0.3	(0.8)	0.2255	1.0	(1.5)	**<0.0001**	0.9	(1.5)	**<0.0001**	3.6	(0.6)	**<0.0001**	0.2	(0.7)
LBD-amygdala (%)	15	(5.1%)	**<0.0001**	2	(0.3%)	**<0.0001**	4	(19.6%)	0.0019	-	(0.0%)	**<0.0001**	331	(28.3%)
FTD-tau (%)	45	(15.3%)	0.1132	254	(33.3%)	**<0.0001**	8	(2.4%)	**<0.0001**	-	(0.0%)	**<0.0001**	136	(11.6%)
FTD-TDP (%)	237	(80.3%)	**<0.0001**	8	(1.0%)	0.0212	2	(0.6%)	0.4490	1	(0.3%)	1.0000	2	(0.2%)
LATE-NC, mean (SD)	2.4	(1.0)	**<0.0001**	0.3	(0.8)	**<0.0001**	1.7	(1.0%)	**<0.0001**	0.7	(1.0)	0.1268	0.6	(0.9)
Hippocampal sclerosis (%)	112	(38.0%)	**<0.0001**	32	(4.2%)	0.0062	26	(99.7)	**<0.0001**	-	(0.0%)	0.0171	23	(2.0%)
Infarcts, mean (SD)	0.1	(0.4)	0.0004	0.3	(0.7)	0.3465	0.3	(0.7)	0.2964	0.1	(0.5)	0.0088	0.2	(0.7)
Microinfarcts, mean (SD)	0.2	(0.6)	0.0005	0.5	(0.9)	0.0913	0.5	(1.0)	0.0253	0.4	(0.8)	0.5441	0.4	(0.9)
Arteriosclerosis, mean (SD)	1.3	(0.9)	**<0.0001**	1.4	(0.9)	0.0008	1.8	(0.9)	**0.0001**	1.4	(0.9)	0.0263	1.6	(0.9)
Atherosclerosis, mean (SD)	0.9	(0.9)	**<0.0001**	1.2	(0.9)	0.9009	1.7	(1.0)	**<0.0001**	1.2	(1.0)	0.5377	1.2	(1.0)
CAA, mean (SD)	0.3	(0.7)	**<0.0001**	0.5	(0.8)	**<0.0001**	1.5	(1.0)	0.1560	1.5	(1.0)	0.6038	1.4	(0.9)
Number of neuropathologies, mean (SD)	5.9	(2.1)	**<0.0001**	5.3	(2.0)	**<0.0001**	8.3	(1.2)	**<0.0001**	7.2	(1.2)	**<0.0001**	6.7	(1.4)
Demographics														
Age at death (years), mean (SD)	72.4	(12.2)	**<0.0001**	81.8	(11.6)	**<0.0001**	84.1	(9.5)	**<0.0001**	77.7	(9.9)	0.0388	79.0	(11.0)
Non-white, n (%)	12	(4.1%)	0.0055	63	(8.3%)	0.4837	33	(10.2%)	0.7024	36	(10.5%)	0.6057	108	(9.3%)
Years of education, mean (SD)	15.9	(2.8)	0.0663	16.1	(3.0)	**0.0002**	15.5	(2.8)	0.9207	15.9	(2.9)	0.0487	15.6	(3.1)
Female (%)	131	(44.4%)	0.0383	305	(40.0%)	**<0.0001**	203	(62.1%)	0.0008	161	(46.4%)	0.1175	600	(51.4%)
# of APOE e4 alleles (%)			**<0.0001**			**<0.0001**			0.4979			0.0489		
0	186	(73.5%)		521	(74.7%)		112	(37.6%)		108	(35.0%)		428	(41.0%)
1+	67	(27.5%)		176	(26.2%)		186	(63.4%)		201	(66.0%)		617	(60.0%)
Primary etiologic diagnosis (%)			**<0.0001**			**<0.0001**			0.0542			**<0.0001**		
AD	67	(22.7%)		242	(31.8%)		294	(89.9%)		266	(76.7%)		981	(84.0%)
LBD	2	(0.7%)		98	(12.9%)		6	(1.8%)		46	(13.3%)		20	(1.7%)
FTLD	200	(67.8%)		180	(23.6%)		13	(4.0%)		22	(6.3%)		86	(7.3%)
Vascular dementia	4	(1.4%)		37	(4.9%)		12	(3.7%)		3	(0.9%)		23	(2.0%)
Other	11	(3.6%)		51	(6.6%)		2	(0.6%)		10	(3.0%)		29	(2.5%)
Not cognitively impaired	11	(3.7%)		154	(20.2%)		-	(0.0%)		-	(0.0%)		29	(2.5%)
MoCA at last visit, mean (SD)	13.4	(5.9)	0.0579	19.2	(7.3)	**<0.0001**	10.6	(5.9)	0.4262	9.6	(7.2)	0.0684	11.3	(7.0)
MMSE at last visit, mean (SD)	17.4	(7.9)	0.3827	22.8	(6.5)	**<0.0001**	15.3	(6.9)	0.3329	15.3	(7.6)	0.3766	16.3	(10.1)
Cognitive status (%)			0.4065			**<0.0001**			0.0164			0.0313		
Cognitively normal	11	(3.7%)		154	(20.2%)		-	(0.0%)		-	(0.0%)		29	(2.5%)
Impaired-not-MCI	-	(0.0%)		14	(1.8%)		-	(0.0%)		2	(0.6%)		6	(0.5%)
MCI	5	(1.7%)		68	(8.9%)		5	(1.5%)		6	(1.7%)		22	(1.9%)
Demented	279	(94.6%)		526	(69.0%)		322	(98.5%)		339	(97.7%)		1,111	(95.1%)

CDR global (%)			0.0481			**<0.0001**			0.1280			**0.0002**		
0	10	(3.4%)		147	(19.3%)		1	(0.3%)		-	(0.0%)		28	(2.4%)
0.5	28	(9.5%)		155	(20.3%)		28	(8.6%)		29	(8.4%)		99	(8.5%)
1	52	(17.6%)		158	(20.7%)		64	(19.6%)		57	(16.4%)		256	(21.9%)
2	79	(26.8%)		132	(17.3%)		114	(34.9%)		102	(29.4%)		378	(32.4%)
3	126	(42.7%)		170	(22.3%)		120	(36.7%)		159	(45.8%)		407	(34.8%)
Age cognitive decline began (years), mean (SD)	62.1	(12.1)	**<0.0001**	71.3	(12.7)	**<0.0001**	71.9	(10.2)	**<0.0001**	67.4	(10.2)	0.2848	68.1	(11.0)
Cognitive symptoms														
Memory (%)	272	(92.5%)	0.0126	572	(75.3%)	**<0.0001**	327	(100.0%)	0.0006	345	(99.4%)	0.0035	1,120	(96.1%)
Orientation (%)	163	(86.7%)	0.0275	340	(62.0%)	**<0.0001**	196	(95.6%)	0.1177	208	(94.1%)	0.3984	715	(92.1%)
Executive function (%)	275	(93.2%)	0.0642	554	(73.2%)	**<0.0001**	320	(97.9%)	0.1451	339	(98.0%)	0.1075	1,116	(96.0%)
Language (%)	245	(83.1%)	0.0597	404	(53.4%)	**<0.0001**	242	(74.7%)	0.2658	298	(86.6%)	0.0005	902	(77.8%)
Visuospatial function (%)	131	(48.0%)	**<0.0001**	276	(38.8%)	**<0.0001**	202	(64.5%)	0.8224	264	(78.6%)	**<0.0001**	721	(65.4%)
Attention (%)	203	(71.5%)	0.0745	330	(45.5%)	**<0.0001**	211	(66.4%)	0.8751	254	(75.1%)	0.0014	729	(65.7%)
Fluctuating cognition (%)	30	(11.1%)	0.7858	115	(16.4%)	0.0086	26	(8.6%)	0.1331	79	(24.3%)	**<0.0001**	130	(11.9%)
Behavioral symptoms														
Apathy (%)	202	(69.2%)	**<0.0001**	348	(46.2%)	0.0547	155	(47.5%)	0.3261	197	(57.9%)	0.0245	588	(50.8%)
Depressed mood (%)	72	(25.4%)	0.0331	224	(30.1%)	0.3656	91	(28.3%)	0.2133	123	(36.7%)	0.1392	368	(32.2%)
Visual hallucinations (%)	14	(5.0%)	0.0002	84	(11.4%)	0.2890	38	(12.3%)	0.7401	91	(27.9%)	**<0.0001**	149	(13.2%)
Auditory hallucinations (%)	7	(2.5%)	0.1221	36	(5.0%)	1.0000	11	(3.6%)	0.4184	27	(8.4%)	0.0218	54	(4.9%)
Delusions (%)	30	(10.8%)	0.0003	80	(10.9%)	**<0.0001**	54	(17.3%)	0.2246	80	(24.4%)	0.1572	231	(20.6%)
Disinhibition (%)	139	(47.4%)	**<0.0001**	141	(18.7%)	0.0041	75	(23.3%)	0.7317	74	(21.7%)	0.3360	282	(24.4%)
Irritability (%)	93	(31.6%)	0.0819	194	(25.9%)	**<0.0001**	96	(29.5%)	0.0118	121	(35.6%)	0.6079	432	(37.3%)
Agitation (%)	88	(29.9%)	0.6765	132	(17.5%)	**<0.0001**	86	(26.5%)	0.0998	108	(31.5%)	1.0000	364	(31.4%)
Personality change (%)	138	(47.1%)	**<0.0001**	124	(16.5%)	0.6514	24	(7.6%)	0.0003	51	(15.0%)	0.8457	180	(15.6%)
Motor symptoms														
Gait disorder (%)	140	(47.6%)	0.0031	359	(48.1%)	**<0.0001**	120	(37.5%)	0.9384	161	(47.5%)	0.0020	434	(37.9%)
Falls (%)	73	(25.0%)	0.2037	254	(34.0%)	**<0.0001**	61	(18.8%)	0.3670	88	(25.7%)	0.1008	244	(21.3%)
Tremors (%)	69	(23.8%)	0.2481	181	(24.2%)	0.0637	55	(17.1%)	0.2034	100	(29.8%)	0.0005	233	(20.5%)
Slowness (%)	148	(51.0%)	**0.0001**	367	(49.0%)	**<0.0001**	121	(37.6%)	0.8763	176	(51.9%)	**<0.0001**	438	(38.3%)
Clinical Dementia Syndrome														
Amnestic multidomain dementia (%)	52	(27.1%)	**<0.0001**	203	(34.9%)	**<0.0001**	182	(88.3%)	0.0058	176	(78.9%)	0.8871	630	(79.6%)
Posterior cortical atrophy (%)	2	(1.0%)	0.0780	4	(0.7%)	0.0004	4	(1.9%)	0.2456	5	(2.2%)	0.3220	31	(3.9%)
Primary progressive aphasia (%)	82	(27.8%)	**<0.0001**	57	(7.5%)	0.9381	8	(2.4%)	0.0022	14	(4.0%)	0.0431	85	(7.3%)
Behavioral variant FTD (%)	127	(43.1%)	**<0.0001**	88	(11.5%)	**<0.0001**	7	(2.1%)	0.5231	14	(4.0%)	0.4314	35	(3.0%)
Lewy body dementia (%)	3	(1.0%)	0.0461	92	(12.1%)	**<0.0001**	9	(2.8%)	0.6687	67	(19.3%)	**<0.0001**	40	(3.4%)
Non-amnestic multidomain dementia (%)	8	(4.2%)	0.0268	32	(5.5%)	**<0.0001**	2	(1.0%)	0.8979	3	(1.3%)	1.0000	11	(1.4%)

P-values are from comparison of each cluster to Cluster 2 (ADNC). Bolding indicates statistically significant differences after Bonferroni correction for multiple comparisons.

Abbreviations: CAA=cerebral amyloid angiopathy; AD=Alzheimer's disease; LBD=Lewy Body Disease; FTLD=frontotemporal lobar degeneration; FTD=frontotemporal dementia; MoCA = Montreal Cognitive Assessment; MMSE = Mini-Mental State Exam; CDR = Clinical Dementia Rating

CHAPTER 3: NEUROPATHOLOGIC FEATURES OF RESISTANCE AND RESILIENCE TO ADNC

3.1 ABSTRACT

Introduction: While Alzheimer's disease neuropathologic change (ADNC) is present in the majority of dementia cases, many individuals with ADNC remain cognitively intact. Understanding why some individuals exhibit resistance (absence of ADNC) or resilience (normal cognition despite ADNC) may illuminate mechanisms of protection against clinical Alzheimer's dementia. Mixed neuropathologies are increasingly recognized as key contributors to cognitive decline and thus may play a role in resistance and resilience.

Methods: We used clinical and autopsy data from the National Alzheimer's Coordinating Center (NACC), including individuals with: intermediate/high ADNC and normal cognition (resilient to ADNC); no/low ADNC, age ≥85, and normal cognition (resistant to ADNC); and intermediate/high ADNC, age ≥65, and cognitive impairment (impaired controls). Multivariable logistic regression assessed associations between non-AD pathologies and resistance/resilience, adjusting for age, sex, education, and APOE ε4 status. We also evaluated longitudinal cognitive trajectories using MoCA and CDR-SB scores.

Results: Among the autopsied participants, 72 were classified as resilient, 107 as resistant, and 1,896 as impaired controls. Resilience was significantly associated with lower Braak stage and lower burden of Lewy body disease (LBD), limbic-predominant age-related TDP-43 encephalopathy neuropathological change (LATE-NC), and arteriosclerosis compared to impaired controls. Resistance was significantly associated with lower burden of amygdala-predominant LBD, frontotemporal lobar degeneration (FTLD)-tau, LATE-NC, hippocampal sclerosis, arteriosclerosis, and cerebral amyloid angiopathy. A higher total burden of pathology was strongly and significantly associated with lower odds of both resistance and resilience. Longitudinal analyses showed no significant difference in cognitive decline between resilient and resistant individuals, suggesting resilient participants maintain stable cognition despite ADNC.

Conclusions: Lower burden of non-AD pathologic disease, including LBD, LATE-NC, cerebrovascular disease, and hippocampal sclerosis, was strongly associated with resistance and resilience to ADNC. These findings emphasize the importance of mixed pathologies in shaping cognitive outcomes and suggest that successful prevention and treatment strategies must address the full spectrum of neurodegenerative and vascular pathology, not just ADNC. Future work should focus on developing biomarkers and interventions for non-ADNC contributors to cognitive decline.

3.2 INTRODUCTION

Alzheimer's neuropathologic disease is present in 60-80% of dementia cases.[19,20,60] Most people with dementia have multiple brain abnormalities at autopsy, including

amyloid plaques, neurofibrillary tangles, Lewy bodies, transactive response DNA binding protein 43 kDa (TDP-43), and cerebrovascular disease.[19,20,60–64] Mixed pathologies may interact to accelerate the onset or progression of cognitive decline, increasing the likelihood of clinical dementia syndrome by up to three times versus a single pathologic disease.[18–20,65] However, presence of neuropathologic disease does not guarantee that an individual will develop dementia before death; most brains from elderly subjects show at least mild pathologic burden of vascular and neurodegenerative disease at autopsy even if dementia was not diagnosed during life.[66,67] A major research question for the field is: how do neuropathology types and burden influence the risk of expressing clinical dementia syndrome, and what factors may influence or confound that risk?

This study applies the lens of mixed pathologies to the study of asymptomatic Alzheimer's disease to increase our understanding of how dementia symptoms develop and how some individuals are able to avoid impaired cognition even at advanced age. Prior studies have investigated the clinical, demographic, and lifestyle characteristics of people who are cognitively normal with severe Alzheimer's disease neuropathologic change (ADNC) (resilient to ADNC) and who never develop ADNC (resistant to ADNC).[68–71] However, many of these studies either did not include other neuropathologic diseases, or did not measure them in relation to Alzheimer's pathology, leaving the connection between resistance/resilience and other pathologies unclear.

Prior studies that examined the influence of non-AD pathology on ADNC resilience include two using the 90+ Study in the oldest old, which found that resilience is associated with lower burden of non-AD pathologies, but noted that associations in this population may differ from younger autopsied populations.[72,73] Two studies using National Alzheimer's Coordinating Center (NACC) data found increased cognitive impairment with increased burden of non-AD pathologies, but did not use resistance or resilience outcome models.[74,75]

A 2019 study using Adult Changes in Thought (ACT)[76] data examined autopsies from a population-based sample, and found that non-Alzheimer's pathologies, especially limbic-predominant age-related TDP-43 encephalopathy neuropathological change (LATE-NC),occurred less frequently in the brains of resistant (no ADNC) and resilient (ADNC but no symptoms) individuals, compared to those with symptomatic Alzheimer's dementia[76]. The sample size was very small (14 resistant, 7 resilient) and longitudinal analyses were limited.[76] Since the ACT study does not assess participants for mild cognitive impairment (MCI), individuals with MCI may have been included in the resistant or resilient group. Lastly, hippocampal sclerosis, now thought to be a distinct entity from the more common LATE-NC[27] was not included. Replicating the applicable part of this study using data from the National Alzheimer's Coordinating Center (NACC) allows for a much larger sample size using the nationwide ADRC program participants, and exclusion of individuals with an MCI diagnosis in the resistant and resilient groups.

We used NACC's expansive standardized clinical and autopsy data to study the subset

of people who die with ADNC but normal cognition. Using these data, we compared cognitively impaired participants with ADNC against those who are cognitively normal with ADNC (resilient to ADNC) or without ADNC (resistant to ADNC) to determine if resilient and resistant individuals have fewer non-Alzheimer's neuropathologic diseases. We also evaluated whether resilient individuals show more cognitive decline than resistant individuals in the years prior to death. Even though both groups are considered clinically to be cognitively normal, resilient individuals may have incipient cognitive decline, indicating that they are not truly unaffected by their ADNC.

3.3 METHODS

Data source

NACC serves as a repository for data from 46 past and present Alzheimer's Disease Research Centers (ADRCs) geographically dispersed across the United States since 2005, with over 54,000 participants. Data are collected by clinicians and trained interviewers at the ADRCs using standardized forms and maintained by NACC as the Uniform Data Set (UDS).[36–38] Longitudinal clinical data are collected from participants and their co-participants (usually a spouse or child) at approximately annual follow-up visits as long as the participant is able. Late-stage subjects who become unable to participate may be followed for autopsy after they discontinue their UDS follow-up visits. Participants have an average of 3.7 visits completed, with two-thirds of participants returning for at least one follow-up visit after their initial visit. Participants with a range of cognitive status (normal to demented) and clinical etiologic diagnoses are included, with 37% of participants having normal cognition at their most recent visit.

Clinical diagnoses and assessments of cognitive status are made by a clinician or a consensus team at each ADRC. Participants come to the ADRCs from a variety of sources according to each ADRC's research focus and protocols, including clinician referral, self-referral, active recruitment through community organizations, and volunteers wanting to contribute to dementia research. Written informed consent was obtained from all participants and their study co-participants; institutional review board (IRB) approval was obtained from all individual ADRCs. Research using the NACC database was approved by the University of Washington IRB.

Over half of all ADRC participants who were followed until death consented to brain autopsy and are included in the neuropathology dataset, which includes standardized data on neuropathologic evaluations performed at the ADRCs according to their own protocols.[40] The NACC neuropathology database was designed by ADRC Neuropathology Core leaders, first implemented in 2002, and has undergone several revisions since to reflect research developments.[40] The dataset contains over 8,000 autopsies, over 5,000 of which reflect the 2012 updated National Institute on Aging-Alzheimer's Association (NIA-AA) guidelines for the neuropathologic assessment of Alzheimer's disease.[77] These guidelines specify an "ABC" score that consists of Thal phases of amyloid deposition ("A"),[78] Braak neurofibrillary tau staging ("B"),[79] and CERAD neuritic plaque score ("C") that have each been converted into four-point severity scales.[80] Together, the ABC score represents the severity level of ADNC: not Alzheimer's disease, low, intermediate, or high ADNC. A 2016 study evaluated the reliability of ABC score using local staining and assessment at ten different ADRCs and

found robustly excellent agreement between ADRCs (average weighted κ =.88, 95% CI: 0.77 – 0.95).[81]

Study population

The study sample was extracted from the March 2025 data freeze of the NACC database. Of the 54,025 participants with a UDS visit, 14,402 were deceased and 8,381 were autopsied (**Figure 3.1**). The study population was limited to the 5,231 participants in the NACC database with a neuropathology form version 10 or later since information on TDP-43 was not collected prior to that version. Participants must either have been diagnosed with dementia prior to autopsy or have their last UDS visit within two years of autopsy. This reduces misclassification of cognitive status at death, as well as reduces selection bias that may occur if participants with rapid cognitive decline (who may be unable to complete UDS visits within two years of death) are excluded. Participants with rare pathologies (Down syndrome, pigment-spheroid degeneration/neurodegeneration with brain iron accumulation (NBIA), multiple system atrophy, trinucleotide repeat disease), malformation of cortical development, metabolic/storage disorder of any type, white matter disease (leukodystrophy, multiple sclerosis or other demyelinating disease), contusion/traumatic brain injury of any type (acute or chronic), neoplasm (primary or metastatic), infectious process of any type (encephalitis, abscess, etc.), herniation (any site), Prion disease, ALS/motor neuron disease (MND), or cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) were excluded. Finally, participants must have been assessed for all neuropathologic features and APOE allele status.

We defined resilient cases as those with intermediate or high ADNC NIA-AA ABC scores and normal cognition at their last UDS visit. Resistant cases are defined as those with no or low ADNC NIA-AA ABC score, normal cognition at their last UDS visit, and age 85 or older at death (**Table 3.1**). The age restriction ensures that participants are old enough at death that we would expect neuropathology to have developed, and we are not simply reflecting a younger population that died from competing risks. Impaired controls for both resistant and resilient groups are defined as participants with intermediate or high ADNC NIA-AA ABC scores, cognitive impairment (MCI or dementia) at their last UDS visit, and age 65 or older at death. (All resilient individuals who met criteria were over 65 at death.) There are 72 resilient, 107 resistant, and 1,888 cognitively impaired participants meeting all criteria.

Neuropathological features

Each ADRC conducted neuropathologic assessments according to its own protocols but following consensus guidelines using the standardized NACC form. We included fourteen neuropathologic variables as covariates in this study, as outlined in **Table 3.2**. In a separate model, we used a simplified total non-AD neuropathology score derived as the sum of each neuropathology variable dichotomized into present vs absent (total score range 0-14).

Clinical characteristics

Demographic characteristics included sex, age at death, years of education, race, and ethnicity. APOE ε4 allele status was classified as none (non-carrier) vs at least one (carrier). APOE genotyping at NACC was obtained from ADGC, the individual ADRCs, the National Centralized Repository for Alzheimer's Disease and Related Dementias (NCRAD), and the NACC Neuropathology Data Set.

Cognitive status (normal cognition, MCI, impaired but not MCI, or dementia) was determined by either a single clinician or consensus group of clinicians at each ADRC. The Montreal Cognitive Assessment (MoCA) was given at assessments where the participant was not too cognitively impaired to complete, with a range of 0-30 (high scores indicating less impairment). The Clinical Dementia Rating (CDR®) Dementia Staging Instrument, a measure of overall level of cognitive impairment and functional ability, was assessed at each UDS visit. The CDR sum of boxes (CDR-SB) summarizes scores over the six domains of the CDR and ranges from 0-18 (higher scores indicating more impairment). The CDR Global is a derived total score calculated from the six domain subscores ranging from 0-3 (higher scores indicating more impairment).

Statistical analysis

We first used descriptive statistics to examine clinical, demographic, and neuropathologic characteristics of resilient and resistant individuals compared to impaired controls.

Using multivariable logistic regression models, we compared the odds of resilience and resistance with non-Alzheimer's pathologic burden. Even though ADNC measures (amyloid plaques and neurofibrillary tau tangles) are part of our definition of resilience, we included these measures to control for levels of ADNC between the resilient and impaired groups. A third model compared the resilient group directly with the resistant group. We adjusted for potential confounders associated with both the independent (level of non-Alzheimer's neuropathologic disease) and dependent (resistance/resilience) variables that may have obscured the true relationship between variables. These confounders include: sex, age at death, years of education, and APOE status (carrier vs non-carrier).[82] In a separate model, we used dichotomized versions of all pathologies (present/absent) to examine the relationship of number of pathologies with resilience and resistance.

We also directly compared the longitudinal cognitive decline of resilient versus resistant cases across UDS visits using MoCA scores (0-30) and the CDR-SB (0-18) from each UDS visit. We modeled the change using general estimating equations for individuals with three or more UDS visits, working backward from the last clinical visit to the initial clinical visit. Models included random effects for repeated measures by participants. Primary predictors were a dichotomous variable for resistance (vs. resilience) and years before death, adjusting for sex, education, and age at death. An interaction term between years and the resistance variable was included to assess the significance of the difference between rates of cognitive decline for resistant vs. resilient groups.

The sample population was restricted to those with a UDS visit within two years of death or a dementia diagnosis. It is possible that unimpaired participants could have developed dementia within two years of death, resulting in misclassification of those individuals as resistant or resilient. To assess the possible impact of this, we performed a sensitivity analysis further restricting the sample to those with a UDS visit within the last year or a dementia diagnosis. To assess the impact of having a minimum age at death of 85 in the resistant group, we performed a second sensitivity analysis lowering the minimum age at death to 75.

All tests were two-sided using $\alpha = 0.05$. Analyses were conducted using R (version 4.5.1).[89]

3.4 RESULTS

Participant characteristics

Demographic and clinical characteristics of resilient, resistant, and impaired control participants are shown in **Table 3.3a**. Resilient participants on average were older at death than impaired controls (89.3 [SD: 6.8] vs 80.7 [SD 10.6]). Resistant participants were older still (91.5 [SD: 4.4]); this was expected given the minimum 85 years age of death inclusion criteria. The resilient group had a higher level of education (16.4 years [SD: 2.7]) compared to the impaired controls (15.7 years [SD: 3.1]). The resistant group was also more likely to be White and non-Hispanic than the impaired controls or resilient group. The impaired controls were far more likely to have at least one APOE e4 allele; the resistant group was less likely than the resilient group to have an APOE e4

allele (15% vs 32%). By definition, the resilient and resistant participants had normal cognition, corresponding with CDR global scores of 0 and high MoCA and MMSE scores. Of the impaired controls, 91.5% had dementia and 8.5% had MCI.

A comparison of neuropathologic features between groups is shown in **Table 3.3b**. Of interest, although both the resilient and impaired control groups were restricted to those with intermediate or high ADNC, the resilient group was more likely to have intermediate ADNC, with impaired controls far more likely to have the highest Thal phase, CERAD score, Braak stage, and resulting ABC score. Resilient and resistant groups had similar levels of LBD severity and LATE-NC severity, which were lower than the impaired controls. All three groups had a similar level of infarcts, microinfarcts, and atherosclerosis, but the resilient and resistant groups showed a lower severity of arteriosclerosis. Resilient participants were more likely to have CAA than resistant participants, who were in turn more likely than the impaired controls.

Hippocampal sclerosis and FTLD-TDP were assessed separately from LATE-NC. Resistant individuals were much less likely to have hippocampal sclerosis than impaired controls. There were no cases of hippocampal sclerosis in the resilient group; this prevented us from including it in our regression analyses for resilient participants. Similarly, there were no cases of FTLD-TDP in either the resistant or resilient groups, so it was excluded from analyses.

Odds of ADNC Resistance and Resilience Associated with Neuropathologic Features

Both main regression models included nine neuropathologic features (LBD stage, amygdala-predominant LBD, FTLD-tau, LATE-NC stage, infarcts, microinfarcts, atherosclerosis, arteriosclerosis, and CAA) adjusted for sex, age at death, years of education, and presence of APOE alleles. The resistant model also included hippocampal sclerosis. In addition, the resilient model also included Thal phase, CERAD neuritic plaque score, and Braak stage, to adjust for the higher distribution of intermediate (vs. high) ABC score among the resilient individuals compared to the impaired controls.

In both models, several neuropathologic features were significantly associated with odds of resistance and/or resilience to ADNC. In the resistant model, having amygdala-predominant LBD, FTLD-tau, higher LATE-NC stage, hippocampal sclerosis, higher arteriosclerosis severity, and higher CAA severity were all associated with decreased odds of resistance to ADNC (**Table 3.4a**). In the resilience model, having higher Braak stage, higher LBD stage, higher LATE-NC stage, and higher arteriosclerosis severity were all associated with decreased odds of resilience to ADNC (**Table 3.4b**).

We also assessed the odds of resistance versus resilience (instead of versus impaired controls) in a separate model that included eight neuropathologic features (LBD stage, amygdala-predominant LBD, LATE-NC stage, infarcts, microinfarcts, atherosclerosis, arteriosclerosis, and CAA), adjusted for sex, age at death, years of education, and

presence of APOE alleles. In this model, only lower severity of CAA was significantly associated with increased odds of resistance versus resilience (**Table 3.4c**).

Separate models replaced individual measures of neuropathologic features with a total neuropathologic severity score ranging from 0-14, still adjusting for sex, age at death, years of education, and APOE status. The resistant model showed that each 1-unit increase in the total score decreased the odds of resistance by 65% (AOR: 0.35; 95% CI: 0.29, 0.42; p-value=<0.001). In the resilient model, each 1-unit increase in the total score decreased the odds of resilience by 35% (AOR: 0.65; 95% CI: 0.55-0.77; p-value=<0.001).

Longitudinal Decline in Resilient Individuals

Comparing the longitudinal cognitive decline of resilient versus resistant cases across UDS visits showed no statistically significant different slope between resilient and resistant individuals (no difference in the time*resistance interaction term) in either the MoCA score (β: -0.117 points; 95% CI: -0.357, 0.103; p=0.297) (**Figure 3.2a**) or the CDR sum of boxes (β: -0.003 points; 95% CI: -0.014, 0.007; p=0.514) (**Figure 3.2b**). Both the MoCA score and CDR-SB showed a statistically significant increase in impairment over time, but this increase did not differ between resilient and resistant groups.

Sensitivity Analyses

Sensitivity analyses restricting the sample population to those with a dementia diagnosis or a UDS visit within the last year (vs. the last two years) reduced the sample population to 46 resilient and 79 resistant individuals. This did not result in any changes regarding which neuropathologic features were significantly associated with odds of resistance or resilience in the main regression models.

Redefining the resistant population as those with no or low ADNC NIA-AA ABC score, normal cognition at their last UDS visit, and age 75 or older at death (vs. age 85 or older at death) increased the number of resistant individuals in the sample from 107 to 159. In the resistant regression model, reducing the minimum age at death resulted in higher LBD stage becoming significantly associated with lower odds of resistance (β: 0.809; 95% CI: 0.692, 0.935; p=0.006), in addition to significant associations from having amygdala-predominant LBD, FTLD-tau, higher LATE-NC stage, hippocampal sclerosis, arteriosclerosis severity, and CAA severity also seen in the main model.

3.5 DISCUSSION

In this study, we examined the neuropathologic associations of cognitive resistance and resilience in older adults, focusing on the roles of non-AD neuropathology in modifying clinical outcomes. Our results provide further evidence that resistance (absence of cognitive impairment with minimal or no ADNC) and resilience (absence of cognitive impairment despite intermediate or high ADNC) are strongly influenced by cooccurring non-AD pathologies.

Among individuals classified as resilient, we observed that a lower burden of Lewy bodies, LATE-NC, and arteriosclerosis was significantly associated with the absence of dementia symptoms. In the resistant group, we found significant associations between cognitive preservation and lower burden of amygdala-predominant LBD, FTLD-tau, LATE-NC, hippocampal sclerosis, arteriosclerosis, and CAA. The associations between resistance and lower burden of amygdala-predominant LBD and CAA are expected, as these pathologies often co-occur with ADNC and may represent early or prodromal stages of Alzheimer's disease.[59,83] In a comparison between the resistant and resilient groups, the only significant difference in neuropathologic features was lower burden of CAA in the resistant group, showing no significant drivers of developing ADNC that were not already known to be associated with ADNC.

We found that total neuropathology score (the sum of dichotomized versions of each of the 14 assessed neuropathologic features) was a strong and statistically significant predictor of both resistance and resilience. This highlights the cumulative effect of multiple neuropathologic processes on cognitive outcomes. Finally, our longitudinal analysis revealed no significant differences in cognitive trajectories between the resilient and resistant groups. This suggests that resilient individuals are not merely on a slower path toward dementia, but are staving off clinical symptoms despite a high burden of ADNC.

Our findings are consistent with and build upon several prior studies that have examined cognitive resilience and resistance using autopsy data. An analysis of data

from the 90+ Study found that the presence of non-AD pathologies increased the odds of a clinical Alzheimer's diagnosis regardless of ADNC burden in the oldest old.[72] Montine et al. extended this work using updated neuropathological assessment guidelines, reporting that resilience was associated with non-ADNC pathologies, particularly LATE-NC, while noting that comorbid influences on cognition may differ in the oldest old compared to younger cohorts.[73] Our findings demonstrate that lower severity of LATE-NC-related pathologies such as TDP-43 and hippocampal sclerosis are also associated with resilience and resistance in a broader age range.

An analysis of ACT cohort data found that individuals with intermediate or high ADNC but minimal non-ADNC had higher resilience.[84] However, the study did not include LATE-NC, which our findings suggest plays a significant role. Another study using ACT data that excluded participants who were not assessed for TDP-43 observed associations between resistance and lower burden of LATE-NC, arteriosclerosis, and CAA, and between resilience and lower burden of LATE-NC and infarcts.[76] The study excluded individuals with MCI from the resistant/resilient groups and had a limited sample size (7 resilient and 14 resistant), which may have reduced power to detect associations.[76] Our larger cohort allowed for detection of significant associations with a wider range of non-ADNC pathologies, even in the presence of MCI. Nevertheless, we identified similar patterns, with LATE and vascular pathologies emerging as key differentiators between symptomatic and asymptomatic individuals, regardless of ADNC burden. Notably, we did not find a statistically significant association between resilience

and infarcts, and found an additional significant association between resilience and Lewy bodies.

Our findings also complement analyses of NACC data by Walker et al. (2022) and White et al. (2023).[74,75] Walker et al. reported that cognitive outcomes were worse in individuals with mixed pathologies, particularly when ADNC was combined with LATE-NC. They also found that cognitively normal individuals were more likely to lack mixed pathology, echoing our finding that lower total pathology burden is associated with both resistance and resilience. White et al., while not explicitly testing resistance/resilience models, observed that greater numbers of neuropathologies were associated with cognitive impairment. Their results similarly suggested that preservation of cognitive function in the presence of ADNC was most common among individuals with fewer comorbid pathologies.

Interestingly, Grodstein et al. (2023) observed that while the prevalence of ADNC has remained stable over time, the prevalence of vascular pathologies has declined, contributing to reduced dementia incidence in more recent cohorts.[85] Although they did not adjust for education or other demographic factors, these results highlight the potential for non-ADNC pathologies to drive population-level trends in cognitive health, consistent with our observations.

Several limitations of this study should be considered. Our sample consisted primarily of white, non-Hispanic, and highly educated participants, limiting the generalizability of our

findings. Neuropathology was assessed at autopsy, and thus may not fully reflect pathology present at the final clinical assessment. Similarly, misclassification of cognitive status is possible if participants have two years between their last assessment and death. To address this, we conducted a sensitivity analysis limiting to participants whose last visit occurred within one year of death, and the results remained consistent. Lastly, autopsied participants represent a self-selected subset of the overall cohort, potentially introducing selection bias if those who consent to autopsy differ systematically from those who do not. However, prior analyses using inverse probability weighting on NACC data have not found substantial changes in results based on this approach,[55] and data from the ACT study suggest that the prevalence of neuropathologies in autopsied dementia cases is generally representative of the full spectrum of clinically diagnosed dementia cases.[56]

Our results have important implications for future research and clinical trial design. The clear associations between resistance/resilience and non-ADNC pathologies suggest that therapeutic approaches focusing solely on amyloid and tau may be insufficient to prevent or delay cognitive decline in many individuals. Rabinovici et al. discussed the various challenges presented by mixed pathologies in clinical trials, including that failure to account for diagnostic heterogeneity can obscure treatment effects, and trials enrolling participants with mixed pathology may require substantially larger sample sizes to detect effects from treatments targeting a single pathology.[16] One potential solution proposed by the authors is screening out participants with co-pathologies, but they note that this could cause high screen failure rates (limiting the number of potential

participants who pass screening eligibility and enroll) and limited generalizability. Trial design must carefully balance pathological specificity with generalizability of results.

In conclusion, our findings reinforce the importance of considering non-ADNC pathologies in both research and clinical contexts. Resistance and resilience to ADNC are strongly associated with the absence or presence of specific comorbid pathologies. These results support a holistic approach to dementia prevention and treatment and highlight the need for improved in vivo biomarkers for non-ADNC processes. Future research should focus on characterizing the biological mechanisms by which these pathologies interact, and how best to identify and treat them in living individuals.

3.6 FIGURES AND TABLES

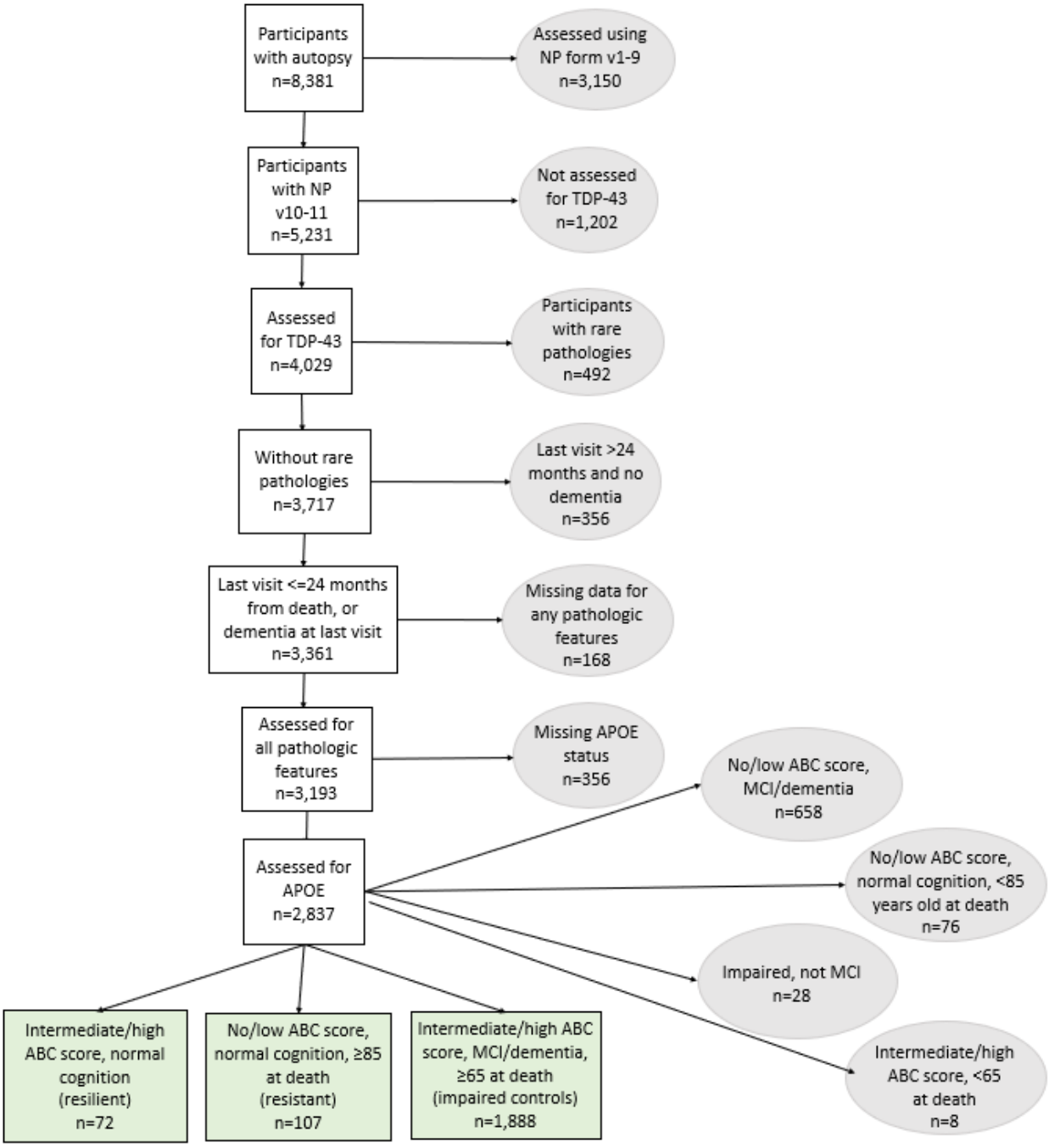

Figure 3.1. Study sample flow diagram. Description of inclusion criteria for the resilient, resistant, and impaired control groups.

Table 3.1: Definitions of Alzheimer's Disease Resistance and Resilience

	Moderate to High ADNC	MCI or Dementia	Non-Alzheimer's Pathologies
Resistant	-	-	+ / -
Resilient	+	-	+ / -
Impaired controls	+	+	+ / -

Table 3.2. Neuropathology Measures

Neuropathology	Measure	Values
Amyloid plaques	Thal phase (A score)[78]	0: Phase 0 1: Phase I 2: Phase II 3: Phase III 4: Phase IV 5: Phase V
	CERAD neuritic plaques score (C score)[80]	0: none 1: sparse 2: moderate 3: frequent
Neurofibrillary tau tangles	Braak stage (B score)[79]	0: Stage 0, not present 1: Stage I 2: Stage II 3: Stage III 4: Stage IV 5: Stage V 6: Stage VI
	presence of FTLD-tau	0: Absent 1: Present
Cerebrovascular	number of gross infarcts	count in cerebral cortex, subcortical cerebral/periventricular white matter, deep cerebral gray matter, internal capsule, brainstem, or cerebellum
	number of microinfarcts	count in cerebral cortex, subcortical or periventricular white matter, subcortical gray matter, or brainstem and cerebellum
	severity of cerebral amyloid angiopathy	0: None 1: Mild 2: Moderate 3: Severe
	severity of arteriosclerosis	0: None 1: Mild 2: Moderate 3: Severe
	severity of atherosclerosis	0: None 1: Mild 2: Moderate 3: Severe
Hippocampal sclerosis	presence of hippocampal sclerosis	0: Absent 1: Present
Lewy body pathology[86]	level of α-synuclein	0: None 1: Olfactory bulb 2: Brainstem-predominant 3: Limbic (transitional) 4: Neocortical (diffuse)
	amygdala-predominant LBD[59]	0: Absent 1: Present
TDP-43	LATE-NC stage[27,87]	0: absent in amygdala 1: localized to amygdala or localized to hippocampus without amygdala 2: extension to hippocampus

		3: extension to the neocortex
	presence of FTLD-TDP	0: Absent 1: Present

Abbreviations: CERAD = Consortium to Establish a Registry for Alzheimer's Disease; FTLD = frontotemporal lobal degeneration; LBD = Lewy Body Disease; TDP = transactive response DNA-binding protein; LATE-NC = limbic-predominant age-related TDP-43 encephalopathy neuropathologic change

Table 3.3a. Demographic and clinical characteristics

	Impaired		Resilient		Resistant	
	Mean (SD) or n (%)		Mean (SD) or n (%)		Mean (SD) or n (%)	
n	1,888		72		107	
Female (%)	965	(51.1%)	40	(55.6%)	59	(55.1%)
Age at death (mean (SD))	80.7	(10.6)	89.3	(6.8)	91.5	(4.4)
Years of education (mean (SD))	15.7	(3.1)	15.7	(2.8)	16.4	(2.7)
Race/ethnicity (%)						
White, non-Hispanic	1,697	(89.9%)	67	(93.1%)	104	(97.2%)
Non-white and/or Hispanic	174	(9.2%)	5	(6.9%)	3	(2.8%)
Unknown	17	(0.9%)	0	(0.0%)	0	(0.0%)
Number of APOE e4 alleles (%)						
0	764	(40.5%)	49	(68.1%)	91	(85.0%)
1	891	(47.2%)	22	(30.6%)	16	(15.0%)
2	233	(12.3%)	1	(1.4%)	0	(0.0%)
Cognitive status (%)						
Normal	0	(0.0%)	72	(100.0%)	107	(100.0%)
MCI	161	(8.5%)	0	(0.0%)	0	(0.0%)
Dementia	1,727	(91.5%)	0	(0.0%)	0	(0.0%)
CDR Global (mean (SD))	1.9	(0.9)	0.0	(0.1)	0.1	(0.3)
MoCA (mean (SD))	11.9	(7.2)	25.1	(3.5)	25.2	(2.5)
MMSE (mean (SD))	17.4	(9)	28.9	(1.1)	28.6	(1.4)

Abbreviations: SD=standard deviation; MoCA = Montreal Cognitive Assessment; MMSE = Mini-Mental State Exam; CDR = Clinical Dementia Rating

Table 3.3b. Neuropathological characteristics

	Impaired		Resilient		Resistant	
	Mean (SD) or n (%)		Mean (SD) or n (%)		Mean (SD) or n (%)	
n	1,888		72		107	
Thal phase (%)						
0	0	(0.0%)	0	(0.0%)	39	(36.4%)
1	7	(0.4%)	2	(2.8%)	27	(25.2%)
2	28	(1.5%)	2	(2.8%)	17	(15.9%)
3	158	(8.4%)	22	(30.6%)	11	(10.3%)
4	408	(21.6%)	30	(41.7%)	8	(7.5%)
5	1,287	(68.2%)	16	(22.2%)	5	(4.7%)
CERAD score (%)						
0 - No neuritic plaques	36	(1.9%)	3	(4.2%)	79	(73.8%)
1 - Sparse neuritic plaques	128	(6.8%)	28	(38.9%)	24	(22.4%)
2 - Moderate neuritic plaques	396	(21.0%)	25	(34.7%)	3	(2.8%)
3 - Frequent neuritic plaques	1,328	(70.3%)	16	(22.2%)	1	(0.9%)
Braak stage (%)						
0	0	(0.0%)	0	(0.0%)	3	(2.8%)
1	0	(0.0%)	0	(0.0%)	17	(15.9%)
2	0	(0.0%)	0	(0.0%)	48	(44.9%)
3	138	(7.3%)	32	(44.4%)	29	(27.1%)
4	215	(11.4%)	21	(29.2%)	9	(8.4%)
5	476	(25.2%)	18	(25.0%)	1	(0.9%)
6	1,059	(56.1%)	1	(1.4%)	0	(0.0%)
NIA-AA ADNC score (ABC score) (%)						
Not ADNC	0	(0.0%)	0	(0.0%)	39	(36.4%)
Low ADNC	0	(0.0%)	0	(0.0%)	68	(63.6%)
Intermediate ADNC	458	(24.3%)	62	(86.1%)	0	(0.0%)
High ADNC	1,430	(75.7%)	10	(13.9%)	0	(0.0%)
LBD stage (%)						
No Lewy body pathology	1,309	(69.3%)	55	(76.4%)	83	(77.6%)
Olfactory bulb	57	(3.0%)	3	(4.2%)	2	(1.9%)
Brainstem-predominant	51	(2.7%)	6	(8.3%)	10	(9.3%)
Limbic (transitional)	195	(10.3%)	5	(6.9%)	8	(7.5%)
Neocortical (diffuse)	276	(14.6%)	3	(4.2%)	4	(3.7%)
LBD amygdala-predominant (%)	353	(18.7%)	4	(5.6%)	1	(0.9%)
FTLD-tau (%)	180	(9.5%)	8	(11.1%)	16	(15.0%)
FTLD-TDP (%)	45	(2.4%)	0	(0.0%)	0	(0.0%)
LATE-NC stage (%)						
None or spinal cord only	1,079	(57.2%)	54	(75.0%)	95	(88.8%)
Amygdala	225	(11.9%)	11	(15.3%)	5	(4.7%)

Hippocampus and/or entorhinal/inferior temporal cortex	436	(23.1%)	4	(5.6%)	3	(2.8%)
Neocortex	148	(7.8%)	3	(4.2%)	4	(3.7%)
Hippocampal sclerosis (%)	326	(17.3%)	0	(0.0%)	3	(2.8%)
Infarcts (mean (SD))	0.3	(0.9)	0.4	(1.1)	0.1	(0.5)
Microinfarcts (mean (SD))	0.5	(1.4)	0.5	(1)	0.4	(1.4)
Atherosclerosis (%)						
None	402	(21.3%)	13	(18.1%)	20	(18.7%)
Mild	752	(39.8%)	32	(44.4%)	41	(38.3%)
Moderate	467	(24.7%)	21	(29.2%)	24	(22.4%)
Severe	267	(14.1%)	6	(8.3%)	22	(20.6%)
Arteriolosclerosis (%)						
None	236	(12.5%)	17	(23.6%)	21	(19.6%)
Mild	675	(35.8%)	27	(37.5%)	49	(45.8%)
Moderate	649	(34.4%)	25	(34.7%)	32	(29.9%)
Severe	328	(17.4%)	3	(4.2%)	5	(4.7%)
Cerebral amyloid angiopathy (CAA) (%)						
None	352	(18.6%)	27	(37.5%)	66	(61.7%)
Mild	756	(40.0%)	28	(38.9%)	29	(27.1%)
Moderate	479	(25.4%)	8	(11.1%)	10	(9.3%)
Severe	301	(15.9%)	9	(12.5%)	2	(1.9%)
Total NP Score (mean (SD))	7.1	(1.5)	6.3	(1.5)	4.7	(1.6)

Abbreviations: SD=standard deviation; ADNC=Alzheimer's disease neuropathologic change, LBD=Lewy Body Disease; FTLD=frontotemporal lobar degeneration; CAA=cerebral amyloid angiopathy; NIA-AA= National Institute on Aging - Alzheimer's Association; LATE-NC= limbic-predominant age-related TDP-43 encephalopathy neuropathological change; NP=neuropathology; CERAD=Consortium to Establish a Registry for Alzheimer's Disease

Table 3.4a. Odds of ADNC Resistance Associated with Neuropathologic Features

Variable	Adj OR	95% CI	p-value
LBD stage	0.88	(0.73-1.05)	0.165
LBD-amygdala	**0.08**	**(0.005-0.39)**	**0.015**
FTLD-tau	**2.39**	**(1.18-4.67)**	**0.013**
LATE stage	**0.42**	**(0.28-0.59)**	**<0.001**
Hippocampal sclerosis	**0.25**	**(0.06-0.78)**	**0.033**
Infarcts	0.75	(0.46-1.09)	0.193
Microinfarcts	0.81	(0.60-1.02)	0.116
Atherosclerosis	0.96	(0.75-1.24)	0.770
Arteriosclerosis	**0.66**	**(0.50-0.87)**	**0.004**
CAA	**0.50**	**(0.36-0.67)**	**<0.001**

Bolded values indicate statistical significance at p=0.05. Adjusted for sex, age at death, education, and APOE. LBD-amygdala, FTLD-tau, and hippocampal sclerosis are dichotomous (present/absent). All other variables are ordinal stage/severity, so the adjusted OR represents the change in odds of resistance associated with increasing one severity level for that neuropathologic feature.

Table 3.4b. Odds of ADNC Resilience Associated with Neuropathologic Features

Variable	Adj OR	95% CI	p-value
Thal phase	0.83	(0.62-1.13)	0.236
CERAD score	0.87	(0.62-1.21)	0.400
Braak stage	**0.34**	**(0.25-0.47)**	**<0.001**
LBD stage	**0.77**	**(0.62-0.94)**	**0.016**
LBD-amygdala	0.57	(0.16-1.55)	0.315
FTLD-tau	0.61	(0.25-1.33)	0.241
LATE stage	**0.64**	**(0.45-0.86)**	**0.005**
Infarcts	1.15	(0.86-1.48)	0.290
Microinfarcts	0.81	(0.60-1.05)	0.140
Atherosclerosis	0.82	(0.60-1.11)	0.208
Arteriosclerosis	**0.55**	**(0.40-0.75)**	**<0.001**
CAA	1.17	(0.87-1.56)	0.288

Bolded values indicate statistical significance at p=0.05. Adjusted for sex, age at death, education, and APOE. LBD-amygdala is dichotomous (present/absent). All other variables are ordinal stage/severity, so the adjusted OR represents the change in odds of resilience associated with increasing one severity level for that neuropathologic feature.

Table 3.4c. Odds of ADNC Resistance vs Resilience Associated with Neuropathologic Features

Variable	Adj OR	95% CI	p-value
LBD stage	0.96	(0.71-1.30)	0.786
LBD-amygdala	0.09	(0.004-0.80)	0.054
LATE stage	0.72	(0.45-2.24)	0.155
Infarcts	0.63	(0.33-1.05)	0.116
Microinfarcts	0.91	(0.67-1.29)	0.468
Atherosclerosis	1.13	(0.79-1.63)	0.493
Arteriosclerosis	1.28	(0.84-1.97)	0.258
CAA	**0.60**	**(0.40-0.88)**	**0.010**

Bolded values indicate statistical significance at p=0.05. Adjusted OR shows odds of neuropathologic feature in resistant group vs the resilient group. Adjusted for sex, age at death, education, and APOE. LBD-amygdala is dichotomous (present/absent). All other variables are ordinal stage/severity, so the adjusted OR represents the change in odds of resistance associated with increasing one severity level for that neuropathologic feature.

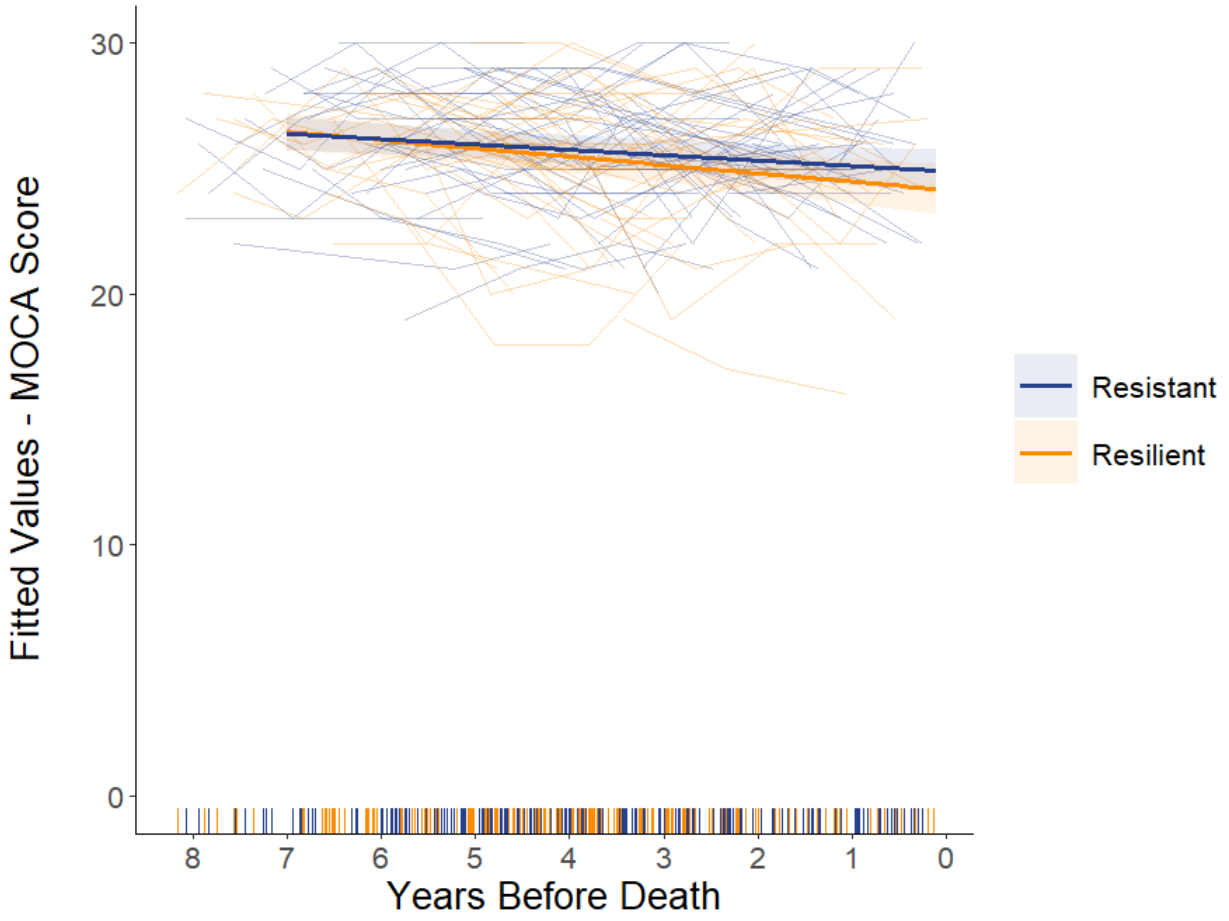

Figure 3.2a. Trajectory of cognitive decline (MoCA score) over time between resistant and resilient groups. Each line represents one individual, with overall linear regression fitted lines in bold.

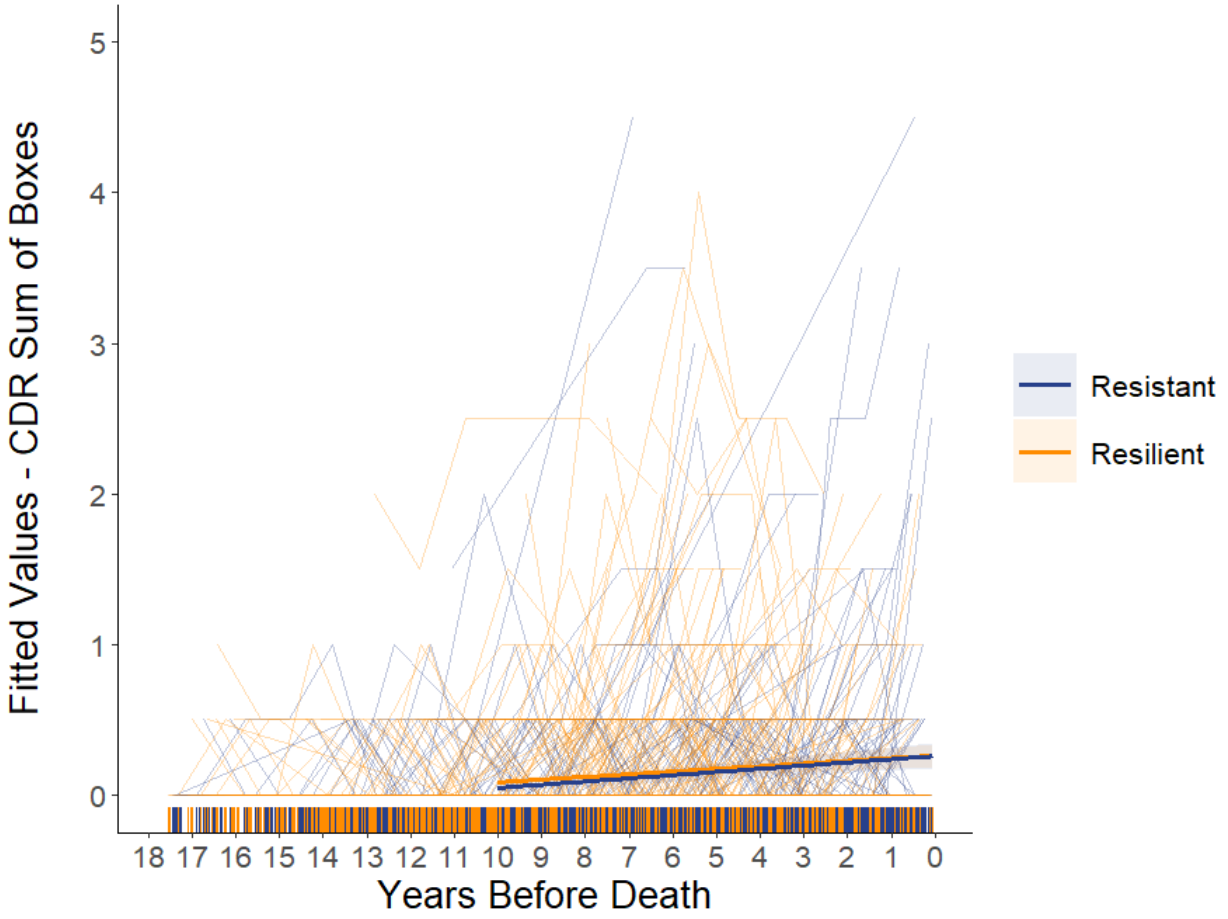

Figure 3.2b. Trajectory of cognitive decline (CDR-SB) over time between resistant and resilient groups. Each line represents one individual, with overall linear regression fitted lines in bold.

CHAPTER 4: NEUROPATHOLOGIC FEATURES OF RESILIENCE TO LATE-NC

4.1 ABSTRACT

Introduction: Limbic-predominant age-related TDP-43 encephalopathy neuropathologic change (LATE-NC) is a common cause of dementia in older adults, frequently co-occurring with other age-related pathologies. However, some individuals maintain normal cognition despite advanced LATE-NC, indicating possible mechanisms of resilience.

Methods: We analyzed autopsy data from two complementary cohorts, the National Alzheimer's Coordinating Center (NACC) and the Adult Changes in Thought (ACT) study, to identify demographic and neuropathologic correlates of cognitive resilience, defined as normal cognition at death despite stage 2 or 3 LATE-NC. Participants aged ≥75 years with stage 2 or 3 LATE-NC were categorized as cognitively resilient or impaired based on final clinical evaluation within two years of death. Multivariable logistic regression assessed associations between twelve neuropathologic features and odds of resilience, stratified by age at death (<90 vs. ≥90 years). In addition, longitudinal Cognitive Abilities Screening Instrument (CASI) scores from ACT participants were used to model rates of cognitive decline.

Results: Across both datasets, 84 resilient and 718 impaired participants met inclusion criteria. Resilient individuals exhibited lower prevalence of Alzheimer's disease neuropathologic change (ADNC), hippocampal sclerosis, and atherosclerosis, and

higher number of infarcts compared with impaired controls. In adjusted models, hippocampal sclerosis was associated with decreased odds of resilience in both age strata, while higher Thal phase and lower number of gross infarcts were also associated with decreased odds of resilience in participants ≥90 years. In the ACT cohort, resilient individuals demonstrated significantly slower annual cognitive decline than impaired controls, although both resilient and impaired groups showed longitudinal decline.

Conclusions: Cognitive resilience to advanced LATE-NC is associated with lower co-occurring ADNC and absence of hippocampal sclerosis, emphasizing the role of mixed pathology in clinical outcomes. Preservation of cognition despite advanced LATE-NC likely reflects protection from effects of amyloid, hippocampal sclerosis, and vascular injury. These findings highlight potential targets for promoting resilience to TDP-43–related neurodegeneration in late life.

4.2 INTRODUCTION

Limbic-predominant age-related TDP-43 encephalopathy neuropathologic change (LATE-NC) is a recently defined proteinopathy that is recognized as common in older adults.[27] LATE-NC is associated with an amnestic dementia syndrome that closely resembles Alzheimer's dementia.[27] Understanding how LATE-NC interacts with other neuropathologic processes is a central challenge in dementia research. Examining resilient individuals who remain cognitively normal despite advanced LATE-NC may offer key insights into mechanisms of cognitive resilience and protection against neurodegenerative disease.

LATE-NC has been strongly associated with cognitive impairment, but the mechanisms underlying individual differences in vulnerability remain unclear.[3,27,88–90] Identifying factors that confer resilience, defined as normal cognition despite advanced LATE-NC, may shed light on protective biological processes that mitigate neurodegenerative damage. Numerous prior studies have focused on resilience to Alzheimer's disease neuropathologic change (ADNC), with evidence suggesting that LATE-NC is an important modifier of cognitive outcomes in Alzheimer's dementia.[73–76] In contrast, little is known about resilience specifically to LATE-NC.

LATE-NC often occurs alongside other age-related pathologies, and these mixed pathologies contribute to more severe cognitive decline.[88,91–95] Hippocampal sclerosis, though frequently co-morbid with LATE-NC, is a separate neuropathologic process, and is neither sufficient nor necessary for a diagnosis of LATE.[27] TDP-43 contributes to cognitive impairment independently of hippocampal sclerosis, but the presence of both further increases the odds of dementia.[96]

Multiple studies have demonstrated that LATE-NC commonly co-occurs with ADNC in older adults, and this combination results in worse cognitive outcomes than either ADNC or LATE-NC alone.[27,95,97,98] For example, although the rate of decline in global cognition in pure LATE-NC is half that of pure ADNC, the rate of decline for mixed LATE-NC + ADNC is twice that of pure ADNC.[97] The relationships between LATE-NC, amyloid, and tau are not fully understood. There may be an interaction between amyloid and TDP-43 given the higher prevalence of TDP-43 co-pathology in combination with

ADNC than in pure tauopathies such as frontotemporal lobar degeneration (FTLD-tau).[95] LATE-NC has also been associated with higher tau burden and higher Braak stage, indicating more extensive neurofibrillary pathology.[76,95,98,99]

Age is another key factor influencing both LATE-NC prevalence and resilience. The frequency of LATE-NC increases every year after age 85.[27,100] Cognitive decline in individuals with mixed ADNC and LATE-NC was observed to be faster among those under 90 years old and slower among those aged 90 and older.[97] Individuals with LATE-NC may harbor different co-pathologies depending on age; one study found that while participants with LATE-NC were more likely to have hippocampal sclerosis and arteriosclerosis, those aged under 90 were also more likely to have ADNC and Lewy Body disease (LBD).[100]

In the present study, we examined neuropathologic and demographic features associated with resilience to LATE-NC, defined as normal cognition despite stage 2 or 3 LATE-NC at autopsy. We leveraged data from two complementary data sources: the National Alzheimer's Coordinating Center (NACC), which aggregates standardized clinical and neuropathologic data from Alzheimer's Disease Research Centers across the United States, and the Adult Changes in Thought (ACT) study, a community-based longitudinal cohort of older adults in the Seattle area. Together, these datasets provide a unique opportunity to identify neuropathologic factors that distinguish cognitively resilient individuals from those who develop dementia in the presence of advanced LATE-NC.

By comparing individuals with advanced LATE-NC who remained cognitively normal ("resilient") to those with dementia ("impaired controls"), we aimed to identify neuropathologic correlates of resilience and to explore how these associations differ across age groups (<90 vs. ≥90 years at death). This work contributes to a growing effort to understand biological and neuropathologic factors that enable cognitive preservation in the face of age-related neurodegeneration.

4.3 METHODS

Data sources

National Alzheimer's Coordinating Center (NACC)

The National Alzheimer's Coordinating Center (NACC) serves as a centralized repository for data collected from 46 past and present Alzheimer's Disease Research Centers (ADRCs) across the United States. Since 2005, NACC has accumulated data on more than 54,000 participants. Demographic, clinical, and neuropsychological data are collected longitudinally using standardized forms in the Uniform Data Set (UDS).[10,101,102] Clinical etiologic diagnoses and cognitive status (ranging from normal cognition to dementia) are determined by a clinician or consensus conference at each ADRC. Participants are recruited through diverse means including clinician referral, community outreach, and self-referral. Written informed consent was obtained from all participants and their study partners; institutional review board (IRB) approval was obtained from each ADRC. Research using the NACC database was separately approved by the University of Washington.

Neuropathologic data are available for more than 8,000 autopsied participants. The NACC neuropathology form was initially implemented in 2002 and has undergone several revisions to reflect advances in the field. The neuropathology data includes standardized neuropathologic evaluations of ADNC, TDP-43, LBD, cerebrovascular lesions, and other neurodegenerative processes performed at the ADRCs according to their own protocols.[103]

Adult Changes in Thought (ACT) Study

The Adult Changes in Thought (ACT) study is a population-based, longitudinal cohort of community-dwelling older adults enrolled through Kaiser Permanente Washington.[11] In contrast to the clinic-based NACC cohort, ACT represents a defined underlying population of older adults receiving routine care. Enrollment occurred in several waves beginning in 1994, with continuous enrollment since 2004. Participants were randomly sampled from health plan members aged 65 years or older and free of dementia at baseline. They were followed biennially until dementia diagnosis, death, or dropout. As of March 2024, 6,206 individuals had completed at least one visit.

Neuropathologic evaluation was performed on over 1,000 participants who died and consented to autopsy. The neuropathologic assessment procedures were standardized and harmonized with ADRC protocols to ensure comparability. The ACT study was approved by the Kaiser Permanente Washington and University of Washington IRBs, with written informed consent from all participants and next-of-kin consent for autopsy.

The University of Washington IRB determined that the use of ACT data in the current study was exempt from review.

Study population

The NACC study population was derived from the September 2025 data freeze. We included 5,386 participants with neuropathology data using version 10 or later forms, as TDP-43 pathology was not recorded prior to that version. Participants with rare or confounding neuropathologies (Down syndrome, pigment-spheroid degeneration/neurodegeneration with brain iron accumulation (NBIA), multiple system atrophy, trinucleotide repeat disease), malformation of cortical development, metabolic/storage disorder of any type, white matter disease (leukodystrophy, multiple sclerosis or other demyelinating disease), contusion/traumatic brain injury of any type (acute or chronic), neoplasm (primary or metastatic), infectious process of any type (encephalitis, abscess, etc.), herniation (any site), Prion disease, ALS/motor neuron disease (MND), or cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) were excluded. Since TDP-43 was recorded by region and not LATE stage in the NACC data, possible overlap with FTLD-TDP is possible. Therefore, participants noted as having FTLD with TDP-43 pathology were excluded from both cases and controls.

The ACT study sample included 260 participants with stage 2 or 3 LATE-NC whose final cognitive assessment occurred within two years of death or who had been clinically

diagnosed with dementia. Participants with probable or definite chronic traumatic encephalopathy (CTE) were excluded.

In both datasets, participants must either have been diagnosed with dementia prior to autopsy or have their last visit within two years of autopsy. This reduces misclassification of cognitive status at death, as well as reduces selection bias that may occur if participants with rapid cognitive decline (who may be unable to complete UDS visits within two years of death) are excluded. Finally, participants must have been assessed for all neuropathologic features and APOE allele status.

We defined **resilient cases** as those who were 75 or older at death with stage 2 or 3 LATE-NC and normal cognition at their last UDS visit. The age restriction reduces the risk of including FTLD-TDP cases (who typically have younger onset) misclassified as LATE-NC. **Impaired controls** were defined as participants with Stage 2 or 3 LATE-NC, dementia at their last UDS visit, and age 75 or older at death (**Figure 4.1**). There are 17 resilient and 532 cognitively impaired participants meeting all criteria from the NACC dataset, and 67 resilient and 186 cognitively impaired participants from the ACT dataset (**Figures 4.2a and 4.2b**).

Neuropathologic and clinical variables

Twelve neuropathologic features were examined as covariates (**Table 4.1**): LATE-NC stage, hippocampal sclerosis, Thal amyloid phase, CERAD neuritic plaque score, Braak neurofibrillary tangle stage, overall LBD stage, amygdala-predominant LBD, gross

infarcts, microinfarcts, atherosclerosis, arteriosclerosis, and cerebral amyloid angiopathy (CAA).

Demographic variables included sex, age at death, race, ethnicity, and years of education. APOE ε4 status was categorized as carrier (≥1 allele) or non-carrier.

In NACC, cognitive status was determined by a single clinician or a consensus conference at each ADRC. In ACT, dementia diagnoses were made at consensus conference if the participant was referred for and completed a diagnostic evaluation for dementia. The Cognitive Abilities Screening Instrument (CASI), ranging from 0 to 100 (higher scores indicating better cognition), was administered biennially to all ACT participants.[104]

Statistical Analysis

Descriptive statistics were used to compare demographic, clinical, and neuropathologic characteristics between resilient individuals and impaired controls. Analyses were conducted separately for NACC and ACT datasets and also for the combined sample. Multivariable logistic regression was used on the combined dataset to estimate the association between neuropathologic features and odds of resilience, stratified by age at death (<90 vs. ≥90 years). Even though LATE-NC stage is part of our definition of resilience, we included this measure to control for level of LATE-NC between the resilient and impaired groups. We adjusted for potential confounders associated with both the independent (level of non-LATE neuropathologic change) and dependent

(resilience) variables that may have obscured the true relationship between variables. These confounders include: sex, age at death, years of education, and APOE status (carrier vs non-carrier).

Since the CASI was administered at each biennial visit in the ACT cohort, we were also able to compare the longitudinal cognitive decline of resilient versus impaired cases across ACT visits using CASI scores from each visit. We modeled the change using general estimating equations for individuals with three or more visits, working backward from the last clinical visit to the initial clinical visit. Models included random effects for repeated measures by participants. Primary predictors were a dichotomous variable for resilience and years before death, adjusting for sex, education, and age at death. An interaction term between years and the resilience variable was included to assess the significance of the difference between rates of cognitive decline for resilient vs. impaired groups. CASI scores were available longitudinally for 151 impaired controls and 58 resilient individuals in the ACT cohort.

All tests were two-sided using $\alpha = 0.05$. Analyses were conducted using R (version 4.5.1).[49]

4.4 RESULTS

Participant Characteristics

Demographic and clinical characteristics of resilient and impaired control participants are shown in Table 4.2a. Overall, impaired controls were far more likely to have at least

one APOE ε4 allele than the resilient group (50.2% vs 26.2%). However, this was primarily reflective of the very high level of APOE in the impaired NACC participants; in the ACT cohort, APOE ε4 prevalence did not differ markedly between groups (35.5% in impaired controls vs. 28.4% in resilient). There were no observed differences in years of education, race, or ethnicity between groups. By design, resilient participants were cognitively normal at their last visit, reflected by higher CASI scores in the ACT cohort.

Neuropathologic Features

Table 4.2b summarizes neuropathologic findings by group. Impaired participants exhibited markedly higher levels of ADNC, including greater Thal phase, CERAD neuritic plaque score, and Braak stage. The prevalence of amygdala-predominant LBD was higher among impaired participants, though the distribution of overall LBD stage did not differ between groups. Hippocampal sclerosis was substantially more frequent in impaired controls across both datasets. Impaired participants also demonstrated more severe atherosclerosis and CAA, whereas the number of gross infarcts was unexpectedly higher among resilient participants in the NACC cohort. Although both groups were restricted to stage 2 or 3 LATE-NC, stage 3 cases were more common among impaired participants in the NACC dataset.

Odds of LATE-NC Resilience

Multivariable regression models were run on the combined NACC and ACT datasets and included all twelve neuropathologic features (LATE-NC stage, hippocampal sclerosis, Thal phase, CERAD score, Braak stage, LBD stage, amygdala-predominant

LBD, gross infarcts, microinfarcts, atherosclerosis, arteriosclerosis, and CAA) adjusted for sex, years of education, and APOE e4 carrier status. LATE-NC stage was included to adjust for the higher prevalence of stage 3 (vs. 2) LATE-NC among the impaired controls relative to the resilient individuals.

Several neuropathologic features were significantly associated with odds of resilience to LATE-NC after adjusting for other neuropathologies. In the ≥90 age of death model, hippocampal sclerosis (AOR: 0.30; 95% CI: 0.13, 0.61; p-value=0.002), higher Thal phase (AOR: 0.71; 95% CI: 0.52, 0.96; p-value=0.030), and lower number of gross infarcts (AOR: 1.40; 95% CI: 1.12,1.80; p-value=0.006) were all associated with decreased odds of resilience to LATE-NC (**Table 4.3a**). In the participants <90 years old, only hippocampal sclerosis (AOR: 0.36; 95% CI: 0.15, 0.93; p-value=0.040) was significantly associated with decreased odds of resilience (**Table 4.3b**). However, CERAD neuritic plaque score was weakly associated (AOR: 0.72; 95% CI: 0.29, 1.01; p-value=0.059). Amygdala-predominant LBD was excluded from the <90 model since there were no resilient individuals with amygdala-predominant LBD, causing instability in model estimates.

Longitudinal Cognitive Decline

Longitudinal analyses of ACT participants revealed significant differences in the trajectory of cognitive decline between resilient and impaired groups. CASI scores decreased over time in both groups, but the annual rate of decline was substantially slower in resilient individuals. The mean difference in annual decline was -0.815 CASI

points (95% CI: –1.024, –0.605; $p < 0.001$), indicating that resilient individuals experienced a more gradual reduction in cognitive function prior to death (**Figure 4.3**).

4.5 DISCUSSION

In this study, we investigated neuropathologic features associated with cognitive resilience (normal cognition despite significant neuropathologic burden) in individuals with advanced (stage 2 or 3) LATE-NC across two large autopsy datasets. Our findings demonstrate that resilience to LATE-NC is influenced by the presence and severity of co-occurring non-LATE pathologies, particularly Alzheimer's disease-related changes, hippocampal sclerosis, and vascular lesions.

Compared to participants with dementia, resilient individuals had lower likelihood of intermediate or high ADNC (Thal phase, Braak stage, CERAD score, and NIA-AA ADNC score). After adjusting for covariates, only lower Thal phase, indicating lower amyloid burden, was significantly associated with increased odds of resilience among individuals 90+ at death. CERAD neuritic plaque score was weakly associated in the <90 age group model. This suggests that amyloid accumulation may play a key role in moderating the clinical effects of TDP-43 pathology, consistent with prior work linking amyloid deposition in the presence of LATE-NC to increased likelihood of cognitive decline.[98]

Hippocampal sclerosis was also strongly associated with reduced odds of resilience in both younger and older age groups, even after adjusting for other neuropathologic

covariates. This aligns with previous studies suggesting an interaction between hippocampal sclerosis and LATE-NC working to exacerbate cognitive decline.[27,96] This has important implications for maintaining resilience in the oldest-old, as both hippocampal sclerosis and TDP-43 are present with substantially higher frequencies at higher ages.[27,96]

Vascular pathology, as measured by the presence of gross infarcts, was unexpectedly associated with *increased* resilience in participants over 90 years old, suggesting that there may a survivorship bias of vascular burden in late life. In contrast, lower burden of gross infarcts has been found to be associated with resilience to ADNC.[76] Interestingly, other cerebrovascular markers, including arteriosclerosis and atherosclerosis, that were more prevalent in individuals resilient to LATE-NC were not significantly related to resilience after multivariable adjustment.

Lewy body pathology showed mixed associations with resilience. Overall Lewy body disease stage did not differ significantly between groups, and was not significantly associated with resilience in either age group after adjustment for covariates. Amygdala-predominant Lewy body pathology was more common among impaired individuals, consistent with prior research suggesting that it frequently co-occurs with early AD pathology and may reflect prodromal Alzheimer's-related processes.[59] After multivariable adjustment, amygdala-predominant LBD was not associated with resilience in the 90+ age group. Since there were no resilient individuals with amygdala-predominant LBD in the <90 age group, we were not able calculate its effect size in the

model. Including it may have shown a significant association with decreased resilience in this group.

Longitudinal analyses in the ACT cohort revealed that while the rate of cognitive decline was significantly slower among resilient individuals, both resilient and impaired participants exhibited decline over time. This indicates that while resilience may delay or attenuate the clinical manifestations of LATE-NC, it does not necessarily confer complete protection from neurodegenerative processes.

Our results are consistent with and extend prior studies on mixed neuropathology and cognitive resilience. Walker et al. (2022) and White et al. (2023) both found that individuals with fewer coexisting pathologies were more likely to maintain normal cognition despite neuropathologic change, in particular mixed ADNC and LATE-NC.[75,105] Surprisingly, we did not detect a statistically significant independent association between tau burden (Braak stage) and resilience after accounting for other co-pathologies, despite prior evidence suggesting that tau and TDP-43 often co-localize and may act synergistically to promote neurodegeneration.[95,99]

Several limitations should be noted. Both NACC and ACT cohorts consist primarily of white, non-Hispanic, and highly educated participants, which may limit generalizability to more diverse populations. Cognitive assessments were performed up to two years before death in some cases, which may have led to misclassification of cognitive status at death. Additionally, as with all autopsy-based research, participants who consent to

autopsy may differ systematically from those who do not, potentially introducing selection bias. However, previous analyses suggest that autopsied participants in both NACC and ACT are broadly representative of their respective cohorts.[55,56]

In conclusion, our findings indicate that cognitive resilience to LATE-NC is in part determined by the absence or lower burden of co-occurring ADNC and hippocampal sclerosis. These results highlight the importance of mixed pathology in shaping clinical outcomes in late life and suggest that interventions targeting these co-pathologies may enhance resilience to TDP-43–related neurodegeneration.

4.6 FIGURES AND TABLES

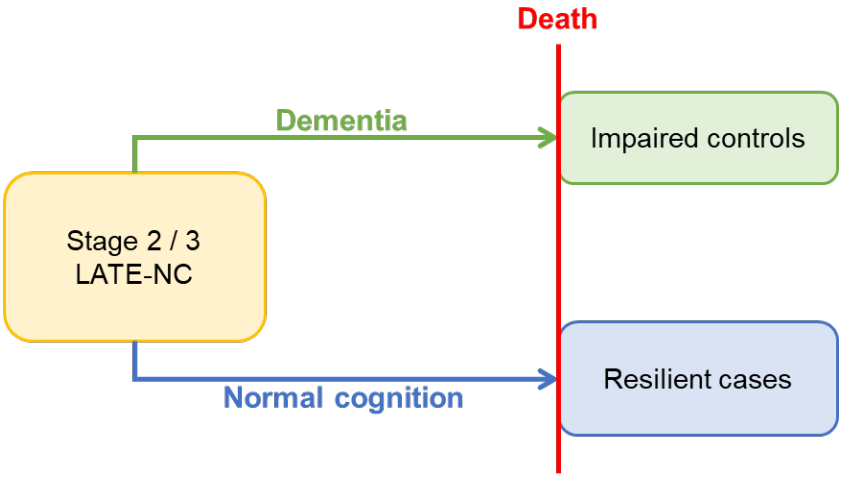

Figure 4.1: Conceptual model of LATE-NC resilience

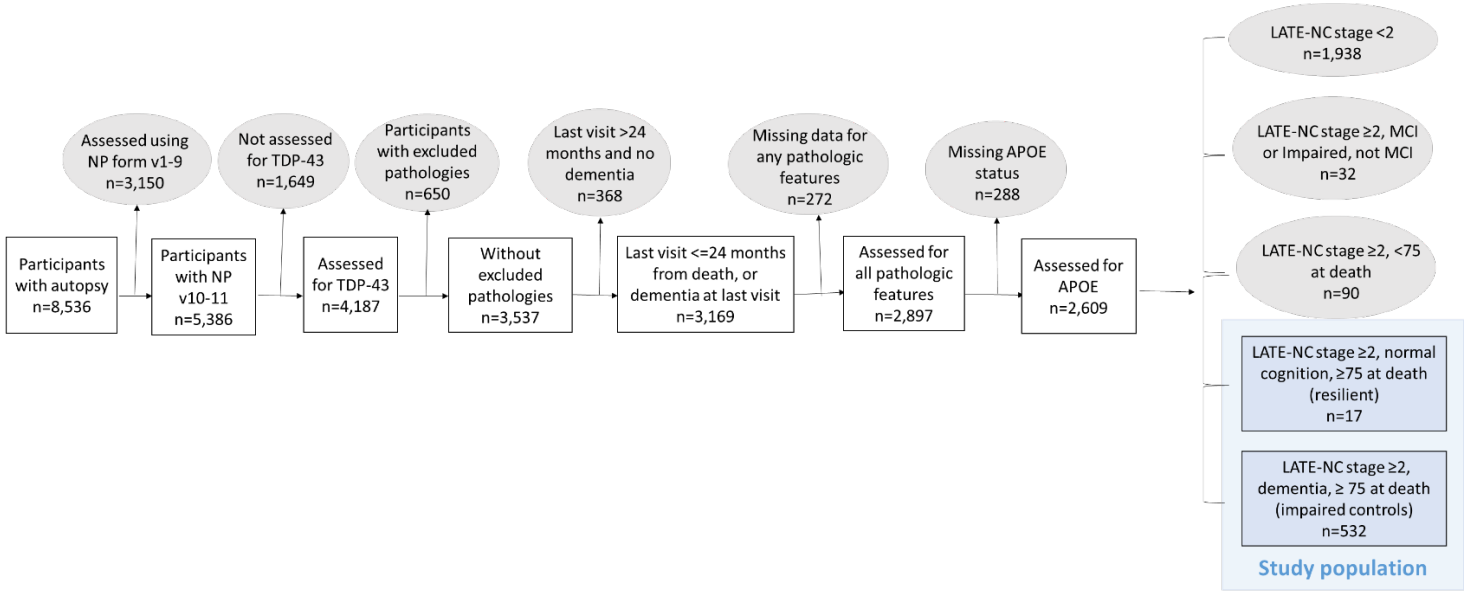

Figure 4.2a: Sample inclusion and exclusion criteria for resilient and impaired control groups (NACC participants)

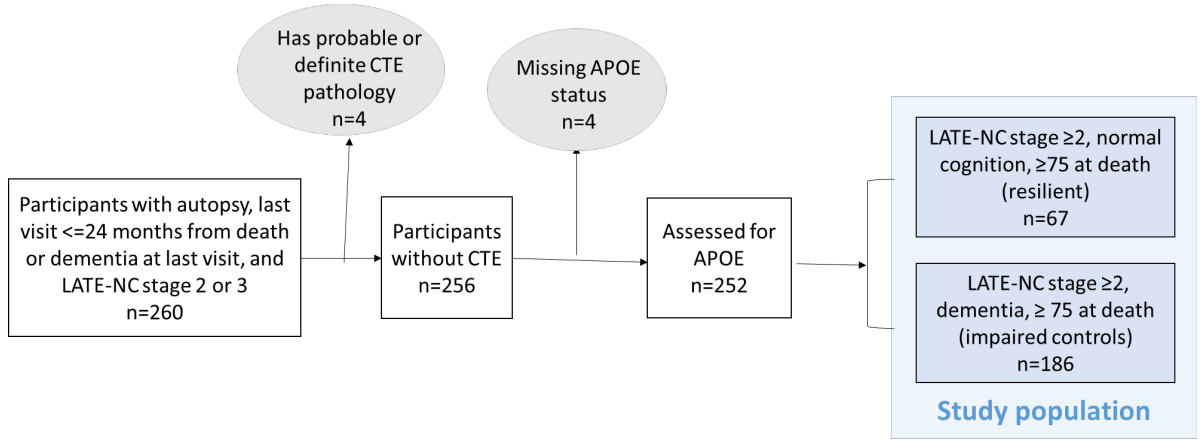

Figure 4.2b: Sample inclusion and exclusion criteria for resilient and impaired control groups (ACT participants)

Table 4.1: Neuropathology Measures

Neuropathology	Measure	Values
Amyloid plaques	Thal phase (A score)[78]	0: Phase 0 1: Phase I 2: Phase II 3: Phase III 4: Phase IV 5: Phase V
	CERAD neuritic plaques score (C score)[80]	0: none 1: sparse 2: moderate 3: frequent
Neurofibrillary tau tangles	Braak stage (B score)[79]	0: Stage 0, not present 1: Stage I 2: Stage II 3: Stage III 4: Stage IV 5: Stage V 6: Stage VI
Vascular brain injury	number of gross infarcts	number of gross infarcts in cerebral cortex, subcortical cerebral/periventricular white matter, deep cerebral gray matter, internal capsule, brainstem, or cerebellum
	number of microinfarcts	number of microinfarcts in cerebral cortex, subcortical or periventricular white matter, subcortical gray matter, or brainstem and cerebellum
	severity of cerebral amyloid angiopathy	0: None 1: Mild 2: Moderate 3: Severe
	severity of arteriosclerosis	0: None 1: Mild 2: Moderate 3: Severe
	severity of atherosclerosis	0: None 1: Mild 2: Moderate 3: Severe
Hippocampal sclerosis	presence of hippocampal sclerosis	0: Absent 1: Present
Lewy body pathology[86]	level of α-synuclein	0: None 1: Olfactory bulb 2: Brainstem-predominant 3: Limbic (transitional) 4: Neocortical (diffuse)
	amygdala-predominant LBD[59]	0: Absent 1: Present
TDP-43	LATE-NC stage[27,87]	0: absent in amygdala 1: localized to amygdala 2: extension to hippocampus 3: extension to the neocortex

Abbreviations: CERAD = Consortium to Establish a Registry for Alzheimer's Disease; FTLD = frontotemporal lobal degeneration; LBD = Lewy Body Disease; TDP = transactive response DNA-binding protein; LATE-NC = limbic-predominant age-related TDP-43 encephalopathy neuropathologic change

Table 4.2a. Demographic and clinical characteristics of study population

	NACC			ACT			Combined		
	Control	Resilient	Overall	Control	Resilient	Overall	Control	Resilient	Overall
	Mean (SD) or n (%)	Mean (SD) or n (%)	Mean (SD) or n (%)	Mean (SD) or n (%)	Mean (SD) or n (%)	Mean (SD) or n (%)	Mean (SD) or n (%)	Mean (SD) or n (%)	Mean (SD) or n (%)
n	532	17	549	189	67	256	721	84	805
Number of APOE e4 alleles (%)									
0	237 (44.5%)	14 (82.4%)	251 (45.7%)	119 (63.0%)	47 (70.1%)	166 (64.8%)	356 (49.4%)	61 (72.6%)	417 (51.8%)
1	250 (47.0%)	3 (17.6%)	253 (46.1%)	61 (32.3%)	17 (25.4%)	78 (30.5%)	311 (43.1%)	20 (23.8%)	331 (41.1%)
2	45 (8.5%)	0 (0.0%)	45 (8.2%)	6 (3.2%)	2 (3.0%)	8 (3.1%)	51 (7.1%)	2 (2.4%)	53 (6.6%)
Age at death (mean (SD))	87 (6.8)	91 (7.6)	87 (6.8)	92 (5.4)	91 (5.1)	92 (5.3)	88 (6.8)	91 (5.6)	89 (6.7)
Race/ethnicity (%)									
White, non-Hispanic	470 (88.3%)	16 (94.1%)	486 (88.5%)	171 (90.5%)	64 (95.5%)	235 (91.8%)	641 (88.9%)	80 (95.2%)	721 (89.6%)
Non-white and/or Hispanic	59 (11.1%)	1 (5.9%)	60 (10.9%)	16 (8.5%)	3 (4.5%)	19 (7.4%)	75 (10.4%)	4 (4.8%)	79 (9.8%)
Unknown	3 (0.6%)	0 (0.0%)	3 (0.5%)	2 (1.1%)	0 (0.0%)	2 (0.8%)	5 (0.7%)	0 (0.0%)	5 (0.6%)
Years of education (mean (SD))	16 (2.9)	16 (2.3)	16 (2.9)	15 (3.1)	15 (3)	15 (3.1)	15 (3)	16 (2.9)	16 (3)
Female (%)	297 (55.8%)	6 (35.3%)	303 (55.2%)	129 (68.3%)	35 (52.2%)	164 (64.1%)	426 (59.1%)	41 (48.8%)	467 (58.0%)
CASI (mean (SD))	NA	NA	NA	77 (10.8)	90 (6.5)	80 (11.4)	77 (10.8)	90 (6.5)	80 (11.4)

Abbreviations: SD=standard deviation; CASI = Cognitive Abilities Screening Instrument

Table 4.2b. Neuropathological characteristics of study population, by data source and combined

	NACC			ACT			Combined		
	Control	Resilient	Overall	Control	Resilient	Overall	Control	Resilient	Overall
	Mean (SD) or n (%)	Mean (SD) or n (%)	Mean (SD) or n (%)	Mean (SD) or n (%)	Mean (SD) or n (%)	Mean (SD) or n (%)	Mean (SD) or n (%)	Mean (SD) or n (%)	Mean (SD) or n (%)
n	532	17	549	189	67	256	721	84	805
Thal phase (%)									
0	15 (2.8%)	3 (17.6%)	18 (3.3%)	12 (6.3%)	9 (13.4%)	21 (8.2%)	27 (3.7%)	12 (14.3%)	39 (4.8%)
1	23 (4.3%)	1 (5.9%)	24 (4.4%)	12 (6.3%)	9 (13.4%)	21 (8.2%)	35 (4.9%)	10 (11.9%)	45 (5.6%)
2	16 (3.0%)	5 (29.4%)	21 (3.8%)	4 (2.1%)	8 (11.9%)	12 (4.7%)	20 (2.8%)	13 (15.5%)	33 (4.1%)
3	41 (7.7%)	5 (29.4%)	46 (8.4%)	29 (15.3%)	14 (20.9%)	43 (16.8%)	70 (9.7%)	19 (22.6%)	89 (11.1%)
4	104 (19.5%)	1 (5.9%)	105 (19.1%)	59 (31.2%)	21 (31.3%)	80 (31.2%)	163 (22.6%)	22 (26.2%)	185 (23.0%)
5	333 (62.6%)	2 (11.8%)	335 (61.0%)	73 (38.6%)	6 (9.0%)	79 (30.9%)	406 (56.3%)	8 (9.5%)	414 (51.4%)
CERAD score (%)									
0 - No neuritic plaques	50 (9.4%)	6 (35.3%)	56 (10.2%)	19 (10.1%)	18 (26.9%)	37 (14.5%)	69 (9.6%)	24 (28.6%)	93 (11.6%)
1 - Sparse neuritic plaques	56 (10.5%)	7 (41.2%)	63 (11.5%)	20 (10.6%)	17 (25.4%)	37 (14.5%)	76 (10.5%)	24 (28.6%)	100 (12.4%)
2 - Moderate neuritic plaques	101 (19.0%)	3 (17.6%)	104 (18.9%)	60 (31.7%)	18 (26.9%)	78 (30.5%)	161 (22.3%)	21 (25.0%)	182 (22.6%)
3 - Frequent neuritic plaques	325 (61.1%)	1 (5.9%)	326 (59.4%)	90 (47.6%)	14 (20.9%)	104 (40.6%)	415 (57.6%)	15 (17.9%)	430 (53.4%)
Braak stage (%)									
0	6 (1.1%)	0 (0.0%)	6 (1.1%)	5 (2.6%)	1 (1.5%)	6 (2.3%)	11 (1.5%)	1 (1.2%)	12 (1.5%)
1	9 (1.7%)	3 (17.6%)	12 (2.2%)	2 (1.1%)	7 (10.4%)	9 (3.5%)	11 (1.5%)	10 (11.9%)	21 (2.6%)
2	32 (6.0%)	3 (17.6%)	35 (6.4%)	5 (2.6%)	7 (10.4%)	12 (4.7%)	37 (5.1%)	10 (11.9%)	47 (5.8%)
3	40 (7.5%)	6 (35.3%)	46 (8.4%)	8 (4.2%)	7 (10.4%)	15 (5.9%)	48 (6.7%)	13 (15.5%)	61 (7.6%)
4	60 (11.3%)	3 (17.6%)	63 (11.5%)	25 (13.2%)	22 (32.8%)	47 (18.4%)	85 (11.8%)	25 (29.8%)	110 (13.7%)
5	153 (28.8%)	2 (11.8%)	155 (28.2%)	72 (38.1%)	19 (28.4%)	91 (35.5%)	225 (31.2%)	21 (25.0%)	246 (30.6%)
6	232 (43.6%)	0 (0.0%)	232 (42.3%)	72 (38.1%)	4 (6.0%)	76 (29.7%)	304 (42.2%)	4 (4.8%)	308 (38.3%)
NIA-AA ADNC score (ABC score) (%)									
Not ADNC	15 (2.8%)	3 (17.6%)	18 (3.3%)	13 (6.9%)	9 (13.4%)	22 (8.6%)	28 (3.9%)	12 (14.3%)	40 (5.0%)
Low ADNC	53 (10.0%)	7 (41.2%)	60 (10.9%)	14 (7.4%)	21 (31.3%)	35 (13.7%)	67 (9.3%)	28 (33.3%)	95 (11.8%)
Intermediate ADNC	109 (20.5%)	6 (35.3%)	115 (20.9%)	47 (24.9%)	24 (35.8%)	71 (27.7%)	156 (21.6%)	30 (35.7%)	186 (23.1%)
High ADNC	355 (66.7%)	1 (5.9%)	356 (64.8%)	115 (60.8%)	13 (19.4%)	128 (50.0%)	470 (65.2%)	14 (16.7%)	484 (60.1%)
LBD stage (%)									
No Lewy body pathology	331 (62.2%)	12 (70.6%)	343 (62.5%)	141 (74.6%)	51 (76.1%)	192 (75.0%)	472 (65.5%)	63 (75.0%)	535 (66.5%)
Olfactory bulb	16 (3.0%)	1 (5.9%)	17 (3.1%)	2 (1.1%)	0 (0.0%)	2 (0.8%)	18 (2.5%)	1 (1.2%)	19 (2.4%)
Brainstem-predominant	24 (4.5%)	2 (11.8%)	26 (4.7%)	2 (1.1%)	1 (1.5%)	3 (1.2%)	26 (3.6%)	3 (3.6%)	29 (3.6%)
Limbic (transitional)	68 (12.8%)	2 (11.8%)	70 (12.8%)	10 (5.3%)	5 (7.5%)	15 (5.9%)	78 (10.8%)	7 (8.3%)	85 (10.6%)
Neocortical (diffuse)	93 (17.5%)	0 (0.0%)	93 (16.9%)	34 (18.0%)	10 (14.9%)	44 (17.2%)	127 (17.6%)	10 (11.9%)	137 (17.0%)
LBD amygdala (%)	86 (16.2%)	0 (0.0%)	86 (15.7%)	20 (10.6%)	1 (1.5%)	21 (8.2%)	106 (14.7%)	1 (1.2%)	107 (13.3%)
LATE-NC stage 3 (%)	133 (25.0%)	6 (35.3%)	139 (25.3%)	20 (10.6%)	3 (4.5%)	23 (9.0%)	153 (21.2%)	9 (10.7%)	162 (20.1%)
Hippocampal sclerosis (%)	240 (45.1%)	2 (11.8%)	242 (44.1%)	103 (54.5%)	18 (26.9%)	121 (47.3%)	343 (47.6%)	20 (23.8%)	363 (45.1%)
Infarcts (mean (SD))	0 (0.8)	1 (3.4)	0 (1)	1 (1.3)	1 (2.4)	1 (1.7)	0 (1)	1 (2.6)	0 (1.3)
Microinfarcts (mean (SD))	1 (1.5)	0 (0.6)	1 (1.4)	1 (1.8)	1 (2.4)	1 (2)	1 (1.6)	1 (2.2)	1 (1.6)
Atherosclerosis (%)									
None	64 (12.0%)	5 (29.4%)	69 (12.6%)	5 (2.6%)	5 (7.5%)	10 (3.9%)	69 (9.6%)	10 (11.9%)	79 (9.8%)
Mild	211 (39.7%)	10 (58.8%)	221 (40.3%)	27 (14.3%)	13 (19.4%)	40 (15.6%)	238 (33.0%)	23 (27.4%)	261 (32.4%)
Moderate	159 (29.9%)	2 (11.8%)	161 (29.3%)	125 (66.1%)	45 (67.2%)	170 (66.4%)	284 (39.4%)	47 (56.0%)	331 (41.1%)
Severe	98 (18.4%)	0 (0.0%)	98 (17.9%)	32 (16.9%)	4 (6.0%)	36 (14.1%)	130 (18.0%)	4 (4.8%)	134 (16.6%)
Arteriolosclerosis (%)									
None	48 (9.0%)	3 (17.6%)	51 (9.3%)	9 (4.8%)	9 (13.4%)	18 (7.0%)	57 (7.9%)	12 (14.3%)	69 (8.6%)
Mild	169 (31.8%)	8 (47.1%)	177 (32.2%)	20 (10.6%)	12 (17.9%)	32 (12.5%)	189 (26.2%)	20 (23.8%)	209 (26.0%)
Moderate	211 (39.7%)	5 (29.4%)	216 (39.3%)	94 (49.7%)	30 (44.8%)	124 (48.4%)	305 (42.3%)	35 (41.7%)	340 (42.2%)
Severe	104 (19.5%)	1 (5.9%)	105 (19.1%)	66 (34.9%)	16 (23.9%)	82 (32.0%)	170 (23.6%)	17 (20.2%)	187 (23.2%)
Cerebral amyloid angiopathy (CAA) (%)									
None	119 (22.4%)	8 (47.1%)	127 (23.1%)	66 (34.9%)	31 (46.3%)	97 (37.9%)	185 (25.7%)	39 (46.4%)	224 (27.8%)
Mild	213 (40.0%)	7 (41.2%)	220 (40.1%)	39 (20.6%)	13 (19.4%)	52 (20.3%)	252 (35.0%)	20 (23.8%)	272 (33.8%)
Moderate	127 (23.9%)	2 (11.8%)	129 (23.5%)	73 (38.6%)	21 (31.3%)	94 (36.7%)	200 (27.7%)	23 (27.4%)	223 (27.7%)
Severe	73 (13.7%)	0 (0.0%)	73 (13.3%)	11 (5.8%)	2 (3.0%)	13 (5.1%)	84 (11.7%)	2 (2.4%)	86 (10.7%)

Abbreviations: SD=standard deviation; ADNC=Alzheimer's disease neuropathologic change, LBD=Lewy Body Disease; CAA=cerebral amyloid angiopathy; NIA-AA= National Institute on Aging - Alzheimer's Association; LATE-NC= limbic-predominant age-related TDP-43 encephalopathy neuropathological change; CERAD=Consortium to Establish a Registry for Alzheimer's Disease

Table 4.3a. Odds of LATE-NC Resilience Associated with Neuropathologic Features, ≥90 Years Age of Death

Variable	Estimate	95% CI	p-value
LATE-NC stage	0.46	(0.14-1.26)	0.159
Hippocampal sclerosis	**0.30**	**(0.13-0.61)**	**0.002**
Thal phase	**0.71**	**(0.52-0.96)**	**0.030**
CERAD score	1.16	(0.71-1.93)	0.564
Braak stage	0.80	(0.58-1.11)	0.177
LBD stage	0.93	(0.73-1.16)	0.519
LBD-amygdala	0.19	(0.01-1.13)	0.133
Gross infarcts	**1.40**	**(1.12-1.80)**	**0.006**
Microinfarcts	1.02	(0.82-1.24)	0.851
Atherosclerosis	0.38	(0.42-1.10)	0.115
Arteriosclerosis	0.71	(0.45-1.11)	0.134
CAA	0.95	(0.63-1.41)	0.807

Bolded values indicate statistical significance at p=0.05. Adjusted for sex, age at death, education, and APOE carrier status. Hippocampal sclerosis and LBD-amygdala is dichotomous (present/absent). All other variables are ordinal stage/severity, so the adjusted OR represents the change in odds of resilience associated with increasing one severity level for that neuropathologic feature.

Table 4.3b. Odds of LATE-NC Resilience Associated with Neuropathologic Features, <90 Years Age of Death

Variable	Estimate	95% CI	p-value
LATE-NC stage	0.05	(0.09-1.14)	0.110
Hippocampal sclerosis	**0.36**	**(0.15-0.93)**	**0.040**
Thal phase	0.31	(0.48-1.10)	0.139
CERAD score	0.72	(0.29-1.01)	0.059
Braak stage	0.89	(0.64-1.26)	0.480
LBD stage	0.85	(0.58-1.00)	0.067
Gross infarcts	0.86	(0.65-1.17)	0.407
Microinfarcts	0.10	(0.86-1.35)	0.471
Atherosclerosis	1.17	(0.61-1.53)	0.876
Arteriosclerosis	1.05	(0.69-1.71)	0.748
CAA	0.79	(0.68-1.83)	0.659

Bolded values indicate statistical significance at p=0.05. Adjusted for sex, age at death, education, and APOE carrier status. Hippocampal sclerosis is dichotomous (present/absent). All other variables are ordinal stage/severity, so the adjusted OR represents the change in odds of resilience associated with increasing one severity level for that neuropathologic feature.

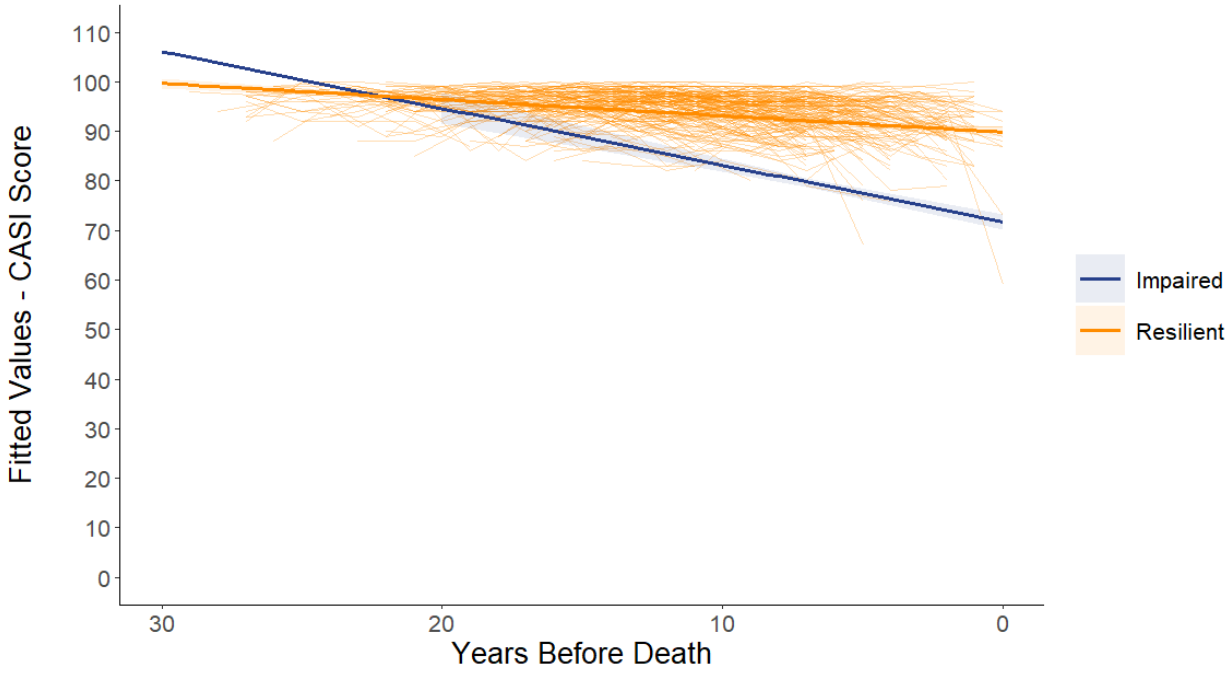

Figure 4.3. Trajectory of cognitive decline (CASI score) over time between impaired and resilient groups. Each line represents one individual, with overall linear regression fitted lines in bold.

CHAPTER 5. CONCLUSIONS

Across all three studies, the interplay among Alzheimer's, TDP-43, α-synuclein, and vascular pathologies emerged as central to explaining variability in cognitive outcomes and clinical presentation. Rather than representing isolated disease entities, these processes coexist and interact in combinations that have distinct biological and clinical correlates.

In Chapter 2, we established that unsupervised data-driven approaches can identify meaningful clusters of neuropathologic disease that recognize known entities such as "pure" ADNC, while also revealing mixed subtypes such as ADNC with LATE and hippocampal sclerosis. These clusters often corresponded to, but did not always match, clinical diagnoses, illustrating the limitations of symptom-based classification. In Chapter 3, we extended this framework by examining how the presence or absence of non-AD pathologies modifies the likelihood of remaining cognitively normal among individuals with or without ADNC. Resilience (normal cognition despite ADNC) was significantly associated with lower Braak stage and lower burden of LBD, LATE-NC, and arteriosclerosis compared to impaired controls. Resistance (normal cognition and no ADNC) was significantly associated with lower burden of amygdala-predominant LBD, FTLD-tau, LATE-NC, hippocampal sclerosis, arteriosclerosis, and cerebral amyloid angiopathy. Total pathology burden was strongly inversely associated with resilience, underscoring the cumulative nature of neuropathologic damage. In Chapter 4, we

further showed that resilience to advanced LATE-NC is similarly dependent on lower burden of other pathologies, namely reduced ADNC and hippocampal sclerosis.

Together, these results underscore the potential pitfalls of treating dementia as a single-pathology or single-disease process. The high prevalence of mixed pathology suggests that current diagnostic boundaries between Alzheimer's disease, Lewy body dementia, and TDP-43–related conditions may oversimplify a complex biological continuum. Clinically, these findings have direct implications for diagnosis and treatment. Many individuals meeting clinical criteria for Alzheimer's dementia likely harbor substantial co-pathology that influences their response to therapy.[16,106] Trials targeting amyloid or tau alone may yield limited benefit in such heterogeneous populations. Incorporating mixed pathology subtyping into clinical trial design could enhance detection of treatment effects. Similarly, identifying resilience-promoting factors may guide development of interventions that bolster cognitive reserve or mitigate the impact of co-pathologies

This dissertation leverages two of the largest, most rigorously characterized autopsy datasets in the world (NACC[11,103] and ACT[11]), allowing robust assessment of multiple pathologies and their clinical correlates. The use of unsupervised clustering and multivariable modeling provides complementary approaches to understanding heterogeneity. However, as with all autopsy-based studies, limitations include potential selection bias, limited racial and socioeconomic diversity, and possible misclassification of cognitive status at death.[56,107] The observational design also precludes causal inference regarding resilience mechanisms; it is possible that the development or

absence of mixed pathologies is a downstream effect of some other aspect of cognitive reserve.

Future research should aim to translate autopsy-derived subtypes and resilience markers into existing and upcoming in vivo biomarkers, enabling identification of mixed pathology profiles during life. Integration of imaging, fluid biomarkers, and genomic data could refine biological subtyping further and illuminate molecular pathways underlying resistance and resilience.[108] Longitudinal studies are needed to determine how individuals develop co-pathologies and whether modifiable risk factors influence cluster membership or resilience due to lower pathologic burden. Expanding representation of diverse racial, ethnic, and socioeconomic groups will be critical for ensuring that biologically defined subtypes are generalizable.

Across three complementary investigations, this dissertation establishes that dementia cannot be understood through single-pathology models. The data reveal coherent subtypes of mixed neuropathologic disease, identify key contributors to resistance and resilience, and highlight the critical influence of cumulative pathology burden on cognitive outcomes. This approach may be valuable for improving diagnostic accuracy and the eventual development of personalized interventions to prevent or mitigate late-life cognitive decline.

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