Effects of Multiple Neuropathologic Features and Their Interactions on Cognitive Performance

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Abstract

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Introduction: Dementia affects millions of Americans with symptoms such as impaired ability to recall, reason, or make decisions. While Alzheimer's Disease (AD) accounts for most dementia cases, multiple neuropathologic features often coexist, complicating diagnosis and treatment. Recent studies have revealed the complexity of neuropathology with the majority of participants exhibiting multiple neuropathologic features, emphasizing the need for a thorough understanding of the association between individual and combinations of neuropathologic features on cognitive performance. This study aims to examine the individual and combined effects of Alzheimer's disease neuropathologic change (ADNC), Lewy body disease (LBD), vascular brain injury (VBI), and limbic predominant, age related, TDP-43 encephalopathy (LATE) on cognitive performance.

Methods: This study used longitudinal clinical visit data and autopsy results from 880 participants from the National Alzheimer's Coordinating Center (NACC) Uniform Data Set (UDS). A linear mixed effects model was used to investigate the effects of neuropathologic

features on cognitive performance across four domains: episodic memory, attention/working memory, semantic memory/language, and executive function. Additionally, interactions between two neuropathologic features were analyzed to determine whether there is an additive effect on cognitive decline.

Results: The rate of decline in overall cognitive performance was fastest among participants in the ADNC + LATE category (-0.46, 95% CI: -0.52, -0.41). The ADNC + LBD category had the fastest decline for attention/working memory (-0.11, CI: -0.14, -0.08), semantic memory/language (-0.19, CI: -0.22, -0.15), and executive function domains (-0.25, CI: -0.30, -0.21). For the episodic memory domain, the fastest decline was seen in the LATE-only category (-0.08, CI: -0.11, -0.06). Less than additive effect was seen for most interactions between two neuropathologic features. The less than additive interaction between ADNC + VBI were all statistically significant across domains, along with ADNC + LATE for episodic memory.

Discussion: Overall, the annual change in z-scores was generally greater for categories with multiple neuropathologic features compared to those with a single feature alone. Among the single neuropathologic features, ADNC had the greatest annual change in all domains except episodic memory, suggesting that ADNC contributes more to cognitive decline than the other neuropathologic features. The variety in trends across domains may also indicate that the effect of neuropathologic features on cognitive performance differ between cognitive domains. The analysis of interactions between ADNC and LBD, VBI, and LATE revealed that most combinations had a slower rate of decline than what would be expected if each neuropathologic feature contributed independently in an additive model. This indicates that the combined effects of these pathologies are not merely additive but involve more complex interactions. The findings highlight the complexity of analyzing the additive effects and their differential impacts on various cognitive domains. Given that the interactions vary between studies, it is crucial to consider multiple neuropathologic features when assessing cognitive decline and dementia.

Introduction

Dementia, characterized by a range of cognitive symptoms such as impaired ability to recall, reason, or make decisions, disrupts daily activities for millions of Americans. The projected prevalence is expected to reach 14 million by 2060[1]. While Alzheimer's disease (AD) is commonly linked to dementia and accounts for 60-80% of dementia cases[2], there are multiple neuropathologic features that contribute to cognitive impairments. Instances of isolated Alzheimer's disease neuropathologic change (ADNC) cases are rare, with evidence of another neuropathologic feature typically present.

A study by Boyle et al found that among 1,079 participants, 78% of the participants had evidence of 2 or more neuropathologic features, 58% having three or more, and only 9% with solely ADNC[3]. Furthermore, the study identified 236 unique combinations of neuropathology. Among their participants, 43% were diagnosed with AD dementia and 25% were diagnosed with MCI at the time of their death[3]. Similarly, a study on 571 brain donors who have been exposed to repetitive head impacts found 252 unique combinations of neuropathologic features[4]. Approximately half (53%) of the participants in this study had dementia at the time of their death[4]. These findings display the heterogeneity and the complexity of neuropathology and highlight the need for a comprehensive understanding of various combinations of neuropathologic features.

Recent studies have analyzed the effect of multiple neuropathologic features on cognitive decline. Neuropathologic comorbidities have shown to display worse cognitive impairments compared to those with only ADNC. For example, results from Gauthreaux et al showed that participants with ADNC and limbic-predominant age-related TDP-43 encephalopathy (LATE) neuropathologic change had significantly worse Clinical Dementia Rating (CDR) global score than those with ADNC alone[5]. This suggests that each neuropathologic feature independently influences cognitive performance. This correlation can also be seen in other neuropathologic combinations such as ADNC plus Lewy body disease (LBD) and ADNC plus microinfarcts[6,7,8].

A study by Brenowitz et al examined the effect of mixed neuropathologic features (ADNC, VBI, and LBD) on cognitive decline using the National Alzheimer's Coordinating Center (NACC) dataset.

Their findings showed that participants with ADNC and LBD had lower initial executive function and faster attention decline compared to other neuropathologic combinations. However, mixed neuropathologies had less than additive effect on cognitive decline[9]. The study by Boyle et al mentioned above also examined independent contributions to cognitive decline for participants with multiple neuropathologic features at a person-specific level.

Building upon the foundation laid by Brenowitz et al., this current study extends on prior work by examining the impact of multiple neuropathologic features including LATE, a feature not previously defined in Brenowitz's study. Additionally, this study serves to cross-check the findings of the study conducted by Boyle et al. The primary objective was to explore the independent effects of neuropathologic features (ADNC, LBD, VBI, and LATE) on cognitive performance in individuals with multiple neuropathologic features. More restrictive definitions of the four neuropathologic features were used to reflect moderate to severe neuropathology. Furthermore, we aimed to explore the interactions between two features to determine if there is an additive effect on cognitive decline.

Methods

Data and Participants

This study was conducted using the Uniform Data Set (UDS) from the National Alzheimer's Coordinating Center (NACC) to investigate the cognitive decline across four domains and overall cognitive performance for each neuropathologic combination. The UDS contains longitudinal data from 2005 from over 30 Alzheimer's Disease Research Centers (ADRCs) funded by the National Institute on Aging (NIA) across the United States[10]. The UDS represents over 48,000 participants with cognitive status ranging from normal cognition to mild cognitive impairment (MCI) to dementia. Participants were recruited in accordance with the protocols established by each ADRC, including clinical referral, self-referral, and active recruitment in community organizations. In many centers, recruitment extends to volunteers with normal cognition. Data from participants and co-participants (a friend or family member) were collected by trained clinicians during in-person office visits, home visits, or telephone calls. The autopsy related variables for this study were obtained from the NACC Neuropathology (NP) Data Set,

which was collected using a standardized neuropathological evaluation. Version 10-11 of the NP dataset includes the 2012 NIA-AA criteria for Alzheimer's disease as well as more detailed information on vascular, TDP-43, and other pathological features[11]. There were two versions of the neuropsychological battery forms that are administered (C1 and C2). The C2 form was implemented in 2015 to replace tests that were used under licensing restrictions (C1).

Participants who are deceased and have undergone autopsy using version 10 or later of the NP form were included in the study, as data on TDP-43 were not collected prior to version 10, which was implemented in 2014. Participants with rare pathologies such as down syndrome, pigment-spheroid degeneration, multiple system atrophy, prion disease, trinucleotide disease, mal formation of cortical development, metabolic storage disorder of any type, white matter disease (leukodystrophy, multiple sclerosis or other demyelinating disease), acute or chronic contusion/ traumatic brain injury of any type, primary or metastatic neoplasm, encephalitis, abscess, or other infectious process of any type, herniation, ALS/motor neuron disease (MND), CADSIL, frontotemporal lobar degeneration (FTLD) with tau, FTLD with TDP43, and other FTLD were excluded from this study in order to eliminate potential confounding. Participants whose last visit occurred over two years before their death were excluded from the study to capture a more accurate representation of the association between the participant's cognitive condition and the neuropathology. In order to examine the longitudinal change in cognitive domains and overall cognitive performance, participants with less than 2 clinical visits were excluded.

Cognitive Performance

The cognitive performance was measured using the scores from the neuropsychological battery form. Each participant had either C1 or C2 test scores for each visit. Neuropsychological battery scores were grouped into four cognitive domains: episodic memory (immediate and delayed WMS-R logical memory or immediate and delayed Craft story 21 recall), attention/working memory (forward and backward digit/number span), semantic memory/ language (category fluency of animals and vegetables and either Boston naming test or multilingual naming test (MINT)), and executive function (trailmaking test part A and B), along with overall cognitive performance score; a measure of overall cognitive

performance (Montreal Cognitive Assessment (MoCA) or Mini-Mental State Examination (MMSE)) (refer to Table 5).

Neuropathologic Features

Neuropathologic features such as Alzheimer's disease neuropathologic change (ADNC), Lewy body disease (LBD), vascular brain injury (VBI), and Limbic predominant, age related, TDP-43 encephalopathy (LATE) were analyzed in this study. Restrictive definitions of the four neuropathologic features were used to reflect moderate to severe neuropathology. ADNC was defined by having intermediate or high ADNC based on the National Institute on Aging and Alzheimer's Association (NIA-AA) ADNC ABC score. ABC score is based on A) Aβ/amyloid plaque score, B) Neurofibrillary tangle score (Braak stage), and C) Neuritic plaque score (CERAD)[12]. LBD was defined by the presence of Lewy body in the neocortical region. VBI was defined by any gross infarct and/or two or more microinfarcts. LATE/TDP-43 was defined by the distribution of TDP-43 immunoreactive inclusions in hippocampus or neocortex. Using those four neuropathologic features, 15 different combinations were created. However, due to small sample size in categories without ADNC and 2 or more neuropathologic features, only 7 categories (ADNC-only, LBD-only, VBI-only, LATE-only, ADNC + LBD, ADNC + VBI, and ADNC + LATE) along with a "no neuropathologic feature" (No NP) category for autopsies with no evidence of the 4 main features were analyzed.

Statistical Analysis

Descriptive statistics were conducted to analyze participant characteristics for each neuropathologic combination. In order to describe the distribution of combinations of neuropathologic features, age, sex (female or male), education (< 16 years vs ≥ 16 years (college graduate)), ethnicity/race (white vs non-white), history of stroke (absent vs present), APOE genotype (present vs absent), cognitive status at the last visit (normal cognition vs impaired no MCI, MCI, or dementia), CDR sum of boxes (SB) at the first and last visit, Braak stage (0-4 vs 5-6), hippocampal sclerosis (none vs unilateral, bilateral, and present but laterality not assessed), severe arteriolosclerosis (none, mild, and moderate vs severe), severe

atherosclerosis (none, mild, and moderate vs severe), and cerebral amyloid angiopathy (none vs mild, moderate, and severe) was analyzed.

A linear mixed effects model was used to estimate the annual change in the cognitive domain z-scores for each neuropathologic category. A categorical variable of the 8 neuropathologic features were used as the independent variable. Random intercepts for ADRC and unique participant ID were included in the model to account for the individual and center-level variations. A domain specific score was calculated by converting individual cognitive test scores into z scores and averaging the scores within each domain. The z-scores were calculated using the mean and the standard deviation of test scores at the initial visits from all participants in the UDS with a global Clinical Dementia Rating (CRD) score of 0 (no impairment). If there was a missing test score, the respective domain score was coded as missing. The same method was used to calculate the overall cognitive performance. The model adjusted for sex, education, age at death, neuropsychological battery form version (c1 or c2), and global CDR score at baseline. To estimate the interaction between two neuropathologic features (e.g. interaction between ADNC and LBD), the 4 main neuropathologic features were recoded into dichotomous variables (e.g. ADNC: 0 or 1) to be used as the independent variable and interaction term. The same covariates and random intercepts were used for the interaction analysis.

Results

Among the 989 participants included in this study, 75.2% had Alzheimer's Disease neuropathologic change (ADNC), 13.7% had Lewy Body Disease (LBD), 22% had vascular brain injury (VBI), and 23.9% had limbic-predominant age-related TDP-43 encephalopathy (LATE). Furthermore, 38.8% of participants had more than one neuropathologic feature (see the breakdown of all the neuropathology categories in Figure 1); 13.7% of participants had no ADNC, LDB, VBI, or LATE neuropathologic features. Following the exclusion of neuropathologic combinations not included in the analysis (LBD + VBI, VBI + LATE, LBD + LATE, and categories with 3 or more features), the sample size was reduced to 880 participants.

As shown in Table 1, the average age at the last visit was 81.5 years old, 8.3 percent of participants were non-Hispanic white, and 65.3 percent had a college degree. The overall average CDR sum of boxes (SB) at the initial visit was 3.05 and 9.8 at the last visit. The ADNC + LBD category had the highest mean CDR-SB at the initial visit (5.1), whereas the ADNC + LATE category had the highest mean at the last visit (13.5), closely followed by ADNC + LBD (13.2). The APOE e4 allele was most prevalent among participants with ADNC + LATE (54.4%).

As shown in the model-based population mean trajectories of cognitive performance of the eight neuropathologic categories, participants with ADNC + LATE had the lowest z-scores across visits in the attention, episodic memory, and semantic memory domains (Figure 2). Participants with ADNC + LBD generally had the lowest z-scores for executive function across visits. The difference between neuropathologic features was less within the attention domain compared to other domains. The ADNC + LATE category also had the lowest z-scores for overall cognitive performance, followed by ADNC-only.

The rate of decline was fastest among participants in the ADNC + LATE category for overall cognitive performance (-0.46, 95% CI: -0.52, -0.41) (Table 3). The ADNC + LBD category had the fastest decline for attention/working memory (-0.11, CI: -0.14, -0.08), semantic memory/language (-0.19, CI: -0.22, -0.15), and executive function domains (-0.25, CI: -0.30, -0.21). For the episodic memory domain, the fastest decline was seen in the LATE-only category (-0.08, CI: -0.11, -0.06). Less than additive effect was seen for most interactions between neuropathologic features. The interaction between ADNC + VBI were all statistically significant across domains, along with ADNC + LATE for episodic memory.

Discussion

The breakdown of neuropathologic categories revealed that only 38.8% of participants had more than one neuropathologic feature. This is due to the restrictive definitions of LBD, VBI, and LATE used for this study. Within the ADNC only group, 13 participants had brainstem-predominant Lewy body pathology, and 116 participants had limbic or amygdala-predominant Lewy body pathology. Additionally, there were 45 participants with TDP-43 inclusions in the amygdala and 41 participants with just one microinfarct among the ADNC only category. Therefore, the percentage of participants with multiple

neuropathologic features would be higher with broader definitions, aligning more closely with the findings of the studies mentioned above.

The analysis of the annual change in z-scores across four cognitive domains and overall cognitive performance revealed several key findings. First, the rate of cognitive decline was greater for participants with ADNC + LBD than for those with LBD alone across all four domains. This pattern was also consistent for VBI and LATE, except for VBI-only vs. ADNC + VBI in executive function and LATE-only vs. ADNC + LATE in episodic memory. When comparing the single neuropathologic features, the ADNC-only category exhibited the greatest rate of cognitive decline in overall cognitive performance and all domains except episodic memory. For episodic memory, the LATE-only and LBD-only categories showed a greater rate of decline than ADNC-only.

Overall, the annual change in z-scores was generally greater for categories with multiple neuropathologic features compared to those with a single feature alone. Among the single neuropathologic features, ADNC had the greatest annual change in all domains except episodic memory, suggesting that ADNC contributes more to cognitive decline than the other neuropathologic features. The variety in trends across domains may also indicate that the effect of neuropathologic features on cognitive performance differ between cognitive domains.

The Boyle et al study examined cognitive decline for individual neuropathologic features. Although the Boyle et al study did not stratify the rate of cognitive decline by cognitive domains, there were some consistencies with the results from this current study. Boyle et al found that AD had the fastest rate of cognitive decline compared to other single neuropathologies, which was true for three of the four domains and overall cognitive performance in this current study.

Additionally, the analysis of interactions between ADNC and LBD, VBI, and LATE revealed that most combinations had a slower rate of decline than what would be expected if each neuropathologic feature contributed independently in an additive model. This indicates that the combined effects of these pathologies are not merely additive but involve more complex interactions.

Comparing the results to the Brenowitz, 2017 study, both studies found that only the less than additive interactions between two neuropathologic features showed statistical significance. The Brenowitz study saw a significant interaction between ADNC + LBD for the memory domain which was not observed in this study. Furthermore, both studies found a significant interaction for ADNC + VBI for the language domain. However, less than additive significant interaction for ADNC + VBI in other domains were only seen in this current study. Based on these comparisons, this current study suggests a broader impact of these interactions across multiple cognitive domains, especially for the ADNC + VBI combination.

Limitations

There was selection bias in this study as participants in the UDS along with those who consent to autopsy are predominantly white and are educated. Specifically, volunteer participants with normal cognition tend to be highly educated. This limits the generalizability of the study as dementia is prevalent across all races and ethnicities and higher levels of education has been shown to be associated with slower cognitive decline[13]. However, education was adjusted for in the regression model to address this issue. The sample size was limited due to the exclusion of previous versions of the neuropathology forms (prior to version 10) in order to be able to assess for TDP-43. Due to the small sample sizes, neuropathologic combinations with more than two categories, along categories that did not include ADNC could not be analyzed for this study. The analysis of the interaction between more than two neuropathologic features may be possible in a future study as the participants who are assessed for TDP-43 increases. Furthermore, this study includes clinical visits from 2005 to 2022, where all the visits prior to March 2015 used the C1 neuropsychological test battery form while subsequent initial visits used the C2 form. Therefore, the two versions of the battery tests may have introduced some bias but was mitigated by using z-scores in reference to the overall sample.

Strengths

One key strength of this study is the availability of longitudinal data on the cognitive status of participants. This longitudinal information enables the analysis of the temporal relationship between

neuropathologic features and cognitive status. Furthermore, the adjustments performed in the analysis help to account for individual variability such as sex and level of education in cognitive trajectories. This study analyzed participants from 31 different ADRCs across the United States, which enhances the generalizability of this study. The diverse geographic representation provides a broader applicability of the study results to a wider population and reduces potential regional biases. Lastly, the data collection methods are standardized across ADRC, providing consistency and reliability of the measurements and improving the validity of the results. Similarly, the autopsies included in this study were more recent as they had to have been assessed for TDP-43. This ensures the use of current standards for identifying neuropathological features and provides a more standard data.

Conclusion

The findings highlight the complexity of analyzing additive effects of neuropathologic features and their differential impacts on various cognitive domains. Given that the interactions vary between studies, it is crucial to consider multiple neuropathologic features when assessing cognitive decline and dementia. It also suggests that future research should aim to clarify these interactions further and assess interactions with more than two neuropathologic features. The findings from this study may influence diagnostic and treatment approaches, emphasizing the need to consider multiple pathologies and their combined effects rather than a single pathology.

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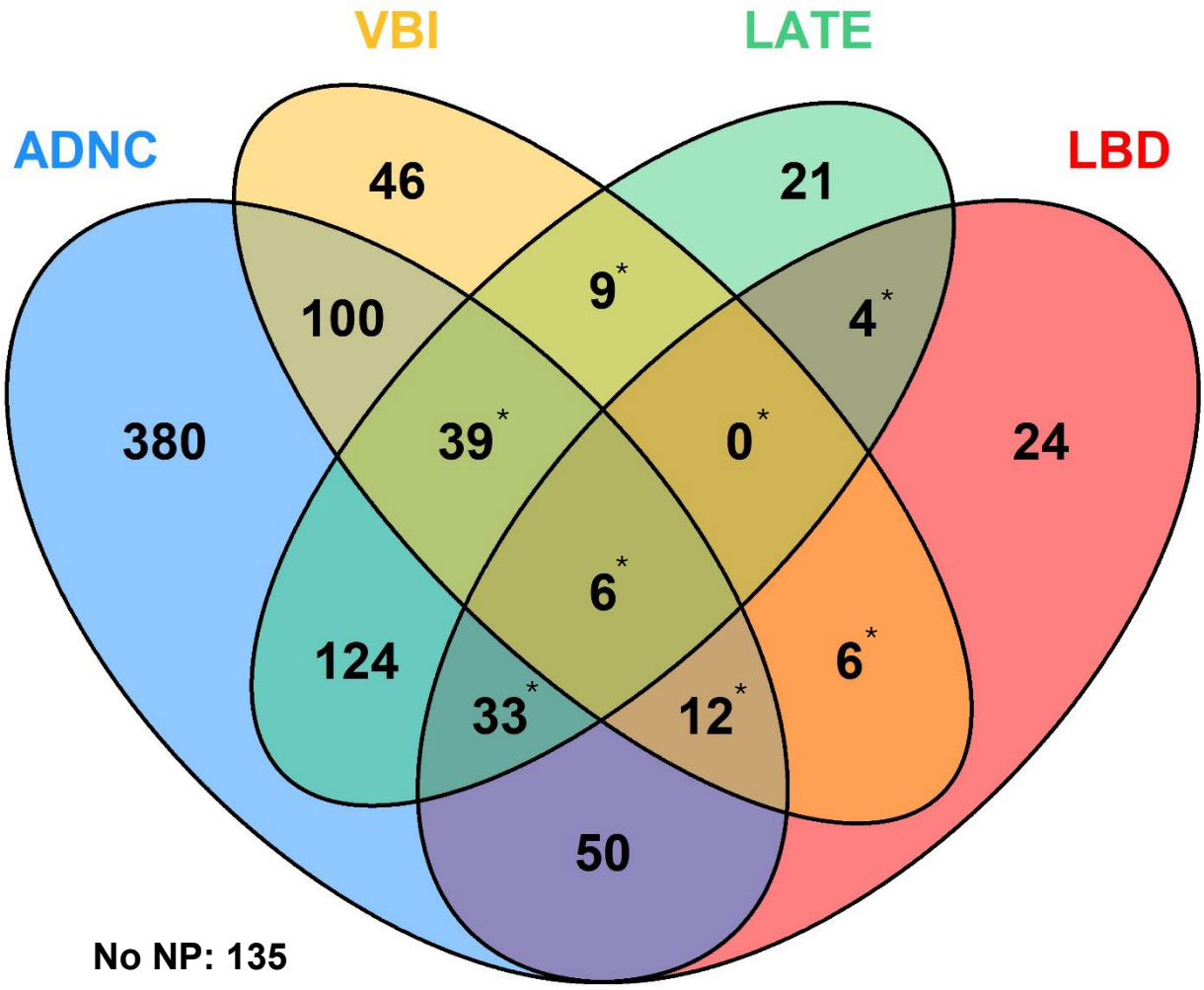
Figure 1. Distribution of selected neuropathologic features (n = 989)



*Excluded from the analysis.
Abbreviations: ADNC = Alzheimer disease neuropathologic change; LATE = limbic predominant, age related, TDP-43 encephalopathy; LBD = Lewy body disease; NP = neuropathology; VBI = vascular brain injury.
Neuropathology definitions: ADNC = intermediate or high NIA-AA Alzheimer's disease neuropathologic change (ADNC) (ABC score); LBD = Lewy body in Neocortical (diffuse) region; VBI = any gross infarct and/or two or more microinfarcts; LATE/TDP-43 = distribution of TDP-43 immunoreactive inclusions in hippocampus or neocortex.

Table 1. Clinical characteristics of participants with autopsy data stratified by ADNC, LBD, VBI, and LATE neuropathologic features

n (%)	Overall	No NP	ADNC Only	LBD Only	VBI Only	LATE Only	ADNC + LBD	ADNC + VBI	ADNC + LATE
Autopsy	880	135	380	24	46	21	50	100	124
Age at death (years), mean (SD)	81.5 (11.0)	83.0 (11.9)	78.5 (11.3)	77.3 (10.7)	84.7 (8.0)	91.7 (7.8)	78.3 (9.5)	85.4 (8.5)	84.6 (9.6)
Female	426 (48.4)	67 (49.6)	191 (50.3)	2 (8.3)	20 (43.5)	10 (47.6)	22 (44.0)	55 (55.0)	59 (47.6)
College graduate	569 (65.0)	93 (68.9)	246 (64.9)	16 (66.7)	25 (58.1)	17 (81.0)	35 (70.0)	50 (50.0)	87 (70.2)
Non-White	71 (8.1)	12 (8.9)	27 (7.1)	0 (0.0)	9 (19.6)	2 (9.5)	4 (8.0)	7 (7.0)	10 (8.2)
History of stroke	17 (1.9)	2 (1.5)	3 (0.8)	0 (0.0)	4 (8.7)	0 (0.0)	0 (0.0)	7 (7.0)	1 (0.8)
APOE e4 allele	297 (36.5)	21 (16.8)	147 (48.5)	6 (27.3)	4 (9.8)	6 (28.6)	16 (50.0)	41 (46.1)	56 (54.4)
CDR-SB at first visit, mean (SD)	3.1 (3.7)	1.0 (2.5)	3.6 (3.7)	3.1 (2.1)	1.6 (2.6)	0.9 (1.8)	5.1 (4.9)	2.8 (3.5)	4.0 (3.9)
CDR-SB at last visit, mean (SD)	9.8 (7.0)	3.2 (5.3)	11.1 (6.7)	10.1 (5.)	5.9 (6.6)	5.3 (5.8)	13.2 (5.0)	10.4 (6.2)	13.5 (5.6)
Cognitive status at the last visit									
Normal cognition	139 (15.8)	74 (54.8)	30 (7.9)	2 (8.3)	13 (28.3)	5 (23.8)	1 (2.0)	9 (9.0)	5 (4.0)
Impaired-not-MCI	16 (1.8)	8 (5.9)	6 (1.6)	0 (0.0)	0 (0.0)	2 (9.5)	0 (0.0)	0 (0.0)	0 (0.0)
MCI	93 (10.6)	17 (12.6)	45 (11.8)	0 (0.0)	8 (17.4)	3 (14.3)	2 (4.0)	10 (10.0)	8 (6.5)
Dementia	632 (71.8)	36 (26.7)	299 (78.7)	22 (91.7)	25 (54.3)	11 (52.4)	47 (94.0)	81 (81.0)	111 (89.5)

Abbreviations: ADNC = Alzheimer disease neuropathologic change; CDR-SB = Clinical Dementia Rating Sum of Boxes; LATE = limbic predominant, age related, TDP-43 encephalopathy; LBD = Lewy body disease; NP = neuropathology; VBI = vascular brain injury.
Neuropathology definitions: ADNC = intermediate or high NIA-AA Alzheimer's disease neuropathologic change (ADNC) (ABC score); LBD = Lewy body in Neocortical (diffuse) region; VBI = any gross infarct and/or two or more microinfarcts; LATE/TDP-43 = distribution of TDP-43 immunoreactive inclusions in hippocampus or neocortex.

Table 2. Pathologic characteristics of participants with autopsy data stratified by ADNC, LBD, VBI, and LATE neuropathologic features

n (%)	Overall	No NP	ADNC Only	LBD Only	VBI Only	LATE Only	ADNC + LBD	ADNC + VBI	ADNC + LATE
Braak stage V and VI	509 (57.8)	1 (0.7)	300 (78.9)	1 (4.2)	1 (2.2)	0 (0.0)	40 (80.0)	62 (62.0)	104 (83.9)
Hippocampal sclerosis	96 (10.9)	3 (2.2)	24 (6.3)	1 (4.2)	5 (10.9)	11 (52.4)	4 (8.0)	6 (6.0)	42 (33.9)
Severe Arteriolosclerosis	127 (14.4)	8 (5.9)	58 (15.3)	5 (20.8)	7 (15.2)	0 (0.0)	4 (8.0)	26 (26.0)	19 (15.3)
Severe Atherosclerosis	108 (12.3)	11 (8.1)	33 (8.7)	2 (8.3)	12 (26.1)	4 (19.0)	2 (4.0)	29 (29.0)	15 (12.1)
Cerebral amyloid angiopathy	584 (66.4)	43 (31.9)	293 (77.1)	7 (29.2)	14 (30.4)	6 (28.6)	39 (78.0)	79 (79.0)	103 (83.1)

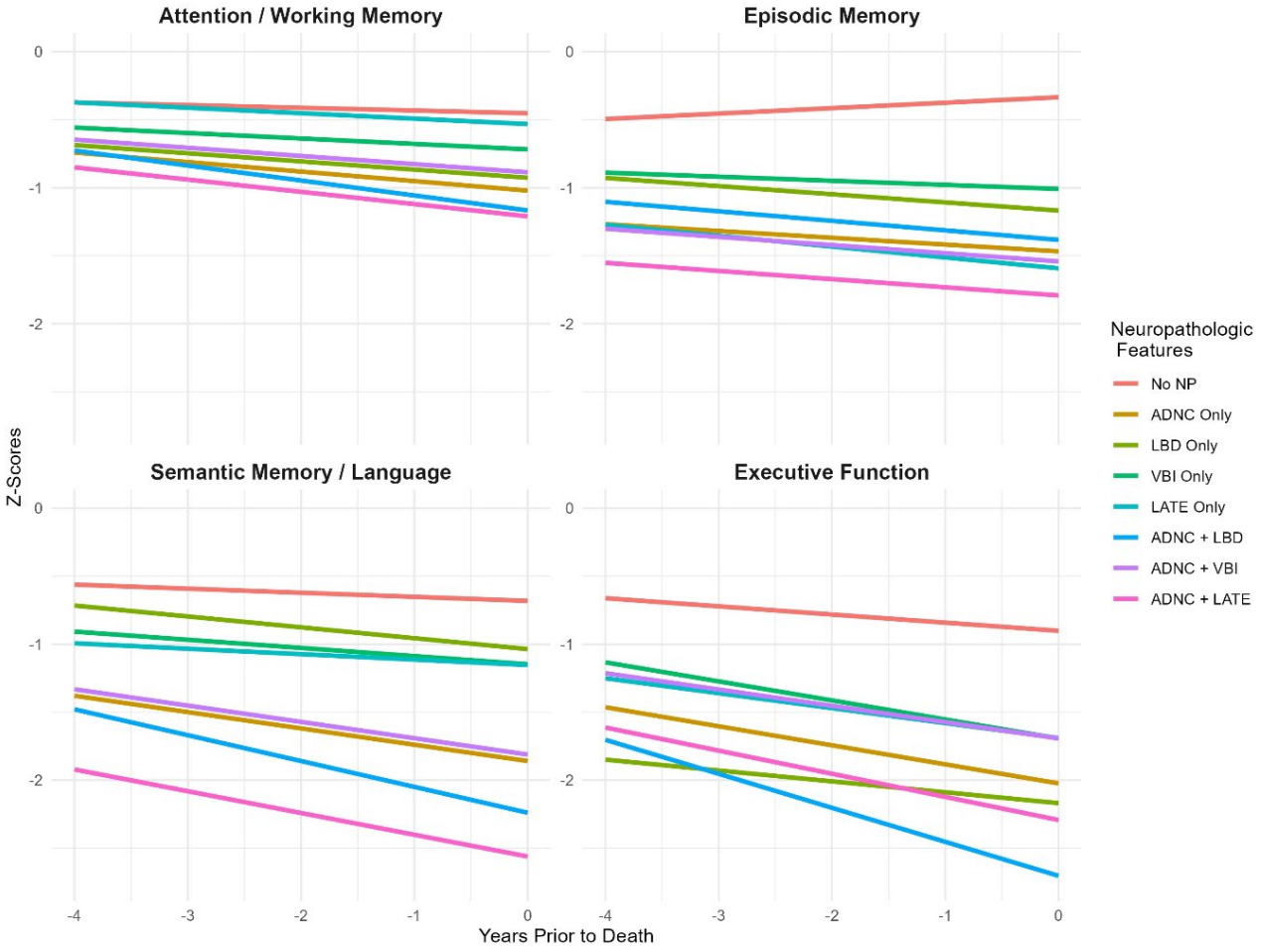
Abbreviations: ADNC = Alzheimer disease neuropathologic change; LATE = limbic predominant, age related, TDP-43 encephalopathy; LBD = Lewy body disease; NP = neuropathology; VBI = vascular brain injury.
Neuropathology definitions: ADNC = intermediate or high NIA-AA Alzheimer's disease neuropathologic change (ADNC) (ABC score); LBD = Lewy body in Neocortical (diffuse) region; VBI = any gross infarct and/or two or more microinfarcts; LATE/TDP-43 = distribution of TDP-43 immunoreactive inclusions in hippocampus or neocortex.

Table 3. Annual change in cognitive domain z scores by neuropathologic features

Cognitive Domains	Neuropathologic Features	Estimate (95% CI) Annual change in z score	Interactions between neuropathologic features
Overall cognitive performance (MMSE or MoCA)	No NP	-0.11 (-0.15, -0.07)	
	ADNC Only	-0.36 (-0.39, -0.33)	
	LBD Only	-0.31 (-0.42, -0.19)	
	VBI Only	-0.30 (-0.37, -0.23)	
	LATE Only	-0.27 (-0.35, -0.20)	
	ADNC + LBD	-0.40 (-0.50, -0.30)	0.03 (-0.10, 0.16)
	ADNC + VBI	-0.34 (-0.39, -0.29)	**0.11 (0.03, 0.19)**
	ADNC + LATE	-0.46 (-0.52, -0.41)	-0.02 (-0.10, 0.06)
Episodic memory	No NP	0.04 (0.02, 0.05)	
	ADNC Only	-0.05 (-0.06, -0.03)	
	LBD Only	-0.06 (-0.10, -0.02)	
	VBI Only	-0.03 (-0.05, -0.01)	
	LATE Only	-0.08 (-0.11, -0.06)	
	ADNC + LBD	-0.07 (-0.10, -0.03)	0.02 (-0.03, 0.06)
	ADNC + VBI	-0.06 (-0.08, -0.05)	**0.02 (0.00, 0.05)**
	ADNC + LATE	-0.06 (-0.08, -0.04)	**0.06 (0.03, 0.09)**
Attention / working memory	No NP	-0.01 (-0.03, -0.01)	
	ADNC Only	-0.07 (-0.08, -0.06)	
	LBD Only	-0.06 (-0.10, -0.03)	
	VBI Only	-0.04 (-0.06, -0.02)	
	LATE Only	-0.04 (-0.07, -0.02)	
	ADNC + LBD	-0.11 (-0.14, -0.08)	0.01 (-0.02, 0.05)
	ADNC + VBI	-0.06 (-0.07, -0.04)	**0.04 (0.02, 0.06)**
	ADNC + LATE	-0.09 (-0.10, -0.07)	0.02 (-0.01, 0.04)
Semantic memory / language	No NP	-0.03 (-0.04, -0.02)	
	ADNC Only	-0.12 (-0.14, -0.11)	
	LBD Only	-0.08 (-0.12, -0.04)	
	VBI Only	-0.06 (-0.08, -0.04)	
	LATE Only	-0.04 (-0.07, -0.02)	
	ADNC + LBD	-0.19 (-0.22, -0.15)	0.01 (-0.03, 0.06)
	ADNC + VBI	-0.12 (-0.14, -0.11)	**0.05 (0.02, 0.07)**
	ADNC + LATE	-0.16 (-0.18, -0.14)	0.00 (-0.02, 0.03)
Executive function	No NP	-0.06 (-0.07, -0.04)	
	ADNC Only	-0.14 (-0.16, -0.13)	
	LBD Only	-0.08 (-0.15, -0.02)	
	VBI Only	-0.14 (-0.17, -0.11)	
	LATE Only	-0.11 (-0.14, -0.07)	
	ADNC + LBD	-0.25 (-0.30, -0.21)	-0.04 (-0.11, 0.03)
	ADNC + VBI	-0.12 (-0.15, -0.10)	**0.09 (0.05, 0.13)**
	ADNC + LATE	-0.17 (-0.20, -0.15)	**0.03 (0.00, 0.07)**

Abbreviations: ADNC = Alzheimer disease neuropathologic change; LATE = limbic predominant, age related, TDP-43 encephalopathy; LBD = Lewy body disease; NP = neuropathology; VBI = vascular brain injury.

Figure 2. Model-Based Sample Mean Trajectories of Cognitive Domain Z Scores



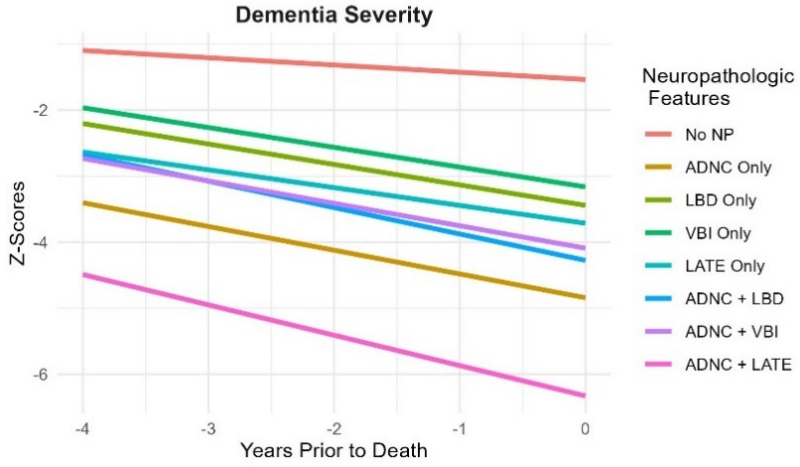


Table 4. Codebook

	Variables Used	Variable Description	Recoded As:
ADNC	NPADNC	NIA-AA Alzheimer's disease neuropathologic change (ADNC) (ABC score)	0 = No (Not AD or low ADNC) 1 = Yes (Intermediate or High ADNC)
LBD	NACCLEWY	Lewy body pathology derived	0 = No Lewy body pathology (no LB, LB in Brainstem-predominant, Limbic (transitional) or amygdala-predominant, Lewy bodies present, but region unspecified or found in the olfactory bulb) 1 = Yes (LB in Neocortical (diffuse))
VBI	NACCINF, NPOLD1, NPOLD2, NPOLD3, NPOLD4	Infarct and lacunes, Number of old microinfarcts, not observed grossly — cerebral cortex, subcortical or periventricular white matter, subcortical gray matter, and brainstem and cerebellum	0 = No (Infarct and lacunes = No and old microinfarcts < 2) 1 = Yes (Infarct and lacunes = Yes and/or two or more old microinfarcts)
LATE	NPTDPC, NPTDPE	Distribution of TDP-43 immunoreactive inclusions — hippocampus or neocortex	0 = No (Hippocampus and neocortex = No) 1 = Yes (hippocampus or neocortex = Yes)
Age at death	NACCDAGE	Age at death	NA
Female	SEX	Subject's sex	0 = Male 1 = Female
College graduate	EDUC	Years of education	0 = Not a college graduate (<16 years) 1 = College graduate (>=16 years) NA = Unknown (99)
Non-White	NACCNIHR	Derived NIH race definitions	0 = White 1 = Non-White (Black or African American, American Indian or Alaska Native, Native Hawaiian or Pacific Islander, Asian, multiracial, unknown or ambiguous)
History of stroke	HXSTROKE	History of stroke	0 = Absent 1 = Present
Cognitively impaired at the last visit	NACCUDSD	Cognitive status at UDS visit	0 = Normal cognition 1 = Impaired (Impaired no MCI, MCI, Dementia)
CDR sum at last visit	CDRSUM	Standard CDR sum of boxes	NA
Braak stage V and VI	NACCBRAA	Braak stage for neurofibrillary degeneration (B score)	0 = (Stage 0-4) 1 = (Stage 5-6)
Hippocampal sclerosis	NPHIPSCL	Hippocampal sclerosis (CA1 and/or subiculum)	0 = None 1 = Unilateral, bilateral, and present but laterality not assessed

Severe Arteriolosclerosis	NACCARTE	Arteriolosclerosis	0 = None, mild, and moderate 1 = Severe
Severe Atherosclerosis	NACCAVAS	Severity of gross findings — atherosclerosis of the circle of Willis	0 = None, mild, and moderate 1 = Severe
Cerebral amyloid angiopathy	NACCAMY	Cerebral amyloid angiopathy	0 = None 1 = Yes (Mild, moderate, and severe)

Table 5. Neuropsychological Test Equivalents in NACC UDS

	Form Versions	
	C1	**C2**
Overall cognitive performance	Mini Mental State Examination (MIMSE)	Montreal Cognitive Assessment (MoCA)
Cognitive Domains		
Episodic memory	WMS-R Logical Memory - Immediate WMS-R Logical Memory - Delayed	Craft Story 21 Recall - Immediate Craft Story 21 Recall - Delayed
Attention / working memory	Digit Span - Forward Digit Span - Backward	Number Span - Forward Number Span - Backward
Semantic memory / language	Boston Naming Test Category fluency (animals, vegetables)	Multilingual Naming Test (MINT) Category fluency (animals, vegetables)
Executive Function	Trailmaking Test Part A Trailmaking Test Part B	Trailmaking Test Part A Trailmaking Test Part B