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TDP-43 Pathology Exacerbates Cognitive Decline in Primary Age-Related Tauopathy

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Abstract

Objective: Primary Age-Related Tauopathy (PART) refers to tau neurofibrillary tangles restricted largely to the medial temporal lobe in the absence of significant beta-amyloid plaques. PART has been associated with cognitive impairment, but contributions from concomitant Limbic Age-Related TDP-43 Encephalopathy neuropathologic change (LATE-NC) are underappreciated.

Methods: We compare prevalence of LATE-NC and vascular co-pathologies in age- and Braak-matched patients with PART (n=45, Braak I-IV, Thal phase 0–2) or early-stage Alzheimer's Disease neuropathologic change (ADNC, n=51, Braak I-IV, Thal 3–5), and examine their influence on clinical and cognitive decline.

Results: Concomitant LATE-NC and vascular pathology were equally common, and cognition was equally impaired, in PART (MMSE=24.8±6.9) and ADNC (MMSE=24.2±6.0). Patients with LATE-NC were more impaired than those without LATE-NC on the MMSE [by 5.8 points; 95%CI: 3.0–8.6], DRS [17.5 points; 7.1–27.9], CDR-sob [5.2 points; 2.1–8.2], Memory composite [0.8 standard deviations (SDs); 0.1–1.6] and Language composite [1.1 SDs; 0.2–2.0], and more likely to receive a dementia diagnosis [odds ratio 4.8; 1.5–18.0]. Those with vascular pathology performed worse than those without on the DRS [by 10.2 points; 0.1–20.3] and Executive composite [1.3 SDs; 0.3–2.3]. Cognition declined similarly in PART and ADNC over 5 years preceding death; however LATE-NC was associated with more rapid decline on the MMSE (β=1.9 [0.9–3.0]), DRS (β=7.8 [3.4–12.7), CDR-sob (β=1.9 [0.4–3.7]), and Language composite (β=0.5 SD [0.1–0.8]), and vascular pathology with more rapid decline on the DRS (β=5.2 [0.6–10.2]).

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Author Contributions:

DSS, DPS, DG, AH contributed to the conception and design of the study. DSS, DPS, DG, DPP, SDE, VG, AH contributed to acquisition and analysis of data. DSS, DPS, DG, SDE, AH contributed to drafting a significant portion of the manuscript or figures.

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All authors have nothing to report.

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Interpretation: LATE-NC, and to a lesser extent vascular co-pathology, exacerbates cognitive impairment and decline in PART and early-stage ADNC.

Introduction:

Primary Age-related Tauopathy (PART) is the neuropathologic designation for tau neurofibrillary tangles restricted to medial temporal lobe, basal forebrain, olfactory bulb and brainstem in the absence of significant beta-amyloid plaques[1]. Although a "tangle-only" form of Alzheimer's disease (AD) has been recognized for decades[2–7], a working classification for PART was not proposed until 2014[1]. This current classification requires Braak stage I-IV tau pathology (i.e., transentorhinal to limbic) with no (Thal Phase 0, "definite PART") or few (Thal Phase 1–2, "possible" PART) amyloid plaques. Several studies suggest that PART, even when restricted to Braak stages I-II, can result in significant cognitive impairment and dementia[1,6,8–12]; however, this cognitive decline is less severe and slower than in typical late-stage AD (i.e., Braak V-VI, Thal phase 3–5)[6,8,10,13]. Whether cognitive decline in PART is less severe or similar to decline associated with early-stage AD neuropathologic change (ADNC) (i.e., Braak stage I-IV, Thal phase 3–5) is open to debate[8,10].

Individuals with PART are on average older than those with AD[1,2,6,14] and may have greater susceptibility to age-related co-pathologies such as Limbic-predominant Aging-related TDP-43 Encephalopathy neuropathologic change (LATE-NC)[15–21] or cerebrovascular pathology. Distinct from TDP-43-associated Frontotemporal Lobar Degeneration (FTLD-TDP), LATE-NC is characterized by neuronal nuclear-to-cytoplasmic translocation of TDP-43, with or without hippocampal sclerosis, and occurs largely in advanced age[20,22,23]. LATE-NC has been associated with cognitive impairment in the presence or absence of significant ADNC[20,24,25], but its effects have not been systematically compared in patients with PART versus early-stage ADNC. Cerebrovascular pathology such as infarcts, microinfarcts, and hemorrhages also increase with age and may contribute to cognitive decline, particularly executive dysfunction, in ADNC and PART[11,26].

The severity of cognitive impairment often observed in individuals with PART is surprising given the low level and localized nature of the tangle pathology, even considering greater than expected hippocampal CA2 region involvement[27] or medial temporal left-right asymmetry[28]. We therefore hypothesized that other age-related co-pathologies such as LATE-NC or vascular pathology may play a significant role in the cognitive decline of these patients. We also hypothesized that, in the presence of low levels of tau pathology, amyloid may contribute to cognitive decline independently of other co-pathologies. However, few studies have compared profiles of cognitive impairment or rates of cognitive decline in patients with PART or early-stage ADNC who have the same degree of tau pathology (Braak stage I-IV) and differ only in level of amyloid plaque pathology (i.e., Thal phase 0–2 vs. Thal phase 3–5), and none have considered potential differential effects of LATE-NC co-pathology. We address these hypotheses by comparing neuropathological features, clinical and cognitive profiles, and rates of cognitive decline in individuals who were found at autopsy to have PART (Braak stage I-IV, Thal phase 0–2) or early-stage ADNC (Braak stage I-IV, Thal phase 3–5), differing only in their degree of amyloid pathology. The impact

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of degree of intrinsic tau pathology is considered across both groups. We also examine the prevalence and contributions of LATE-NC and vascular co-pathologies to the clinical and cognitive phenotypes of PART and early-stage ADNC.

Methods:

Standard Protocol Approvals, Registrations, and Patient Consent.

The research protocol was reviewed and approved by the human subjects review board at the University of California, San Diego (UCSD). Informed consent was obtained from all patients or their caregivers consistent with California State law.

Participants.

All individuals autopsied at the UCSD Shiley-Marcos Alzheimer's Disease Research Center (ADRC) who met criteria for PART (i.e., Braak stage I-IV, low amyloid burden) or early-stage ADNC (i.e., Braak stage I-IV, high amyloid burden) were identified. Cases were initially identified based on Thal phasing[29] or CERAD neuritic plaque score[30] as a proxy for amyloid burden. Participants were included in these cohorts without regard to LATE-NC or cerebrovascular pathology, but were excluded if they did not have sufficient clinical and cognitive data for analysis or if they had a pathologic diagnosis of FTLD (FTLD-tau or FTLD-TDP43), Lewy Bodies in the brainstem, limbic and neocortical regions, or any other neuropathologic condition that could result in neurologic impairment (e.g. Creutzfeldt-Jakob Disease, Multiple Sclerosis). Lewy Bodies were not systematically assessed in the amygdala, as "amygdala-predominant" Lewy Body Disease is generally only seen in cases with more advanced ADNC than included in this study[31], and has not been shown to significantly affect cognition[32,33]. All cases with PART and an equal number of randomly selected cases with ADNC in the same age and Braak stage range as the PART cases were included in the final sample. Case selection was blind to all other clinical information and presence or degree of LATE-NC or cerebrovascular pathology. During the retrospective pathologic workup, participants were dropped if tissue unavailability precluded full LATE-NC staging or Thal phasing, and several were re-classified from PART to ADNC when retrospective Thal phasing was complete. The final sample, therefore, included 44 PART cases and 52 ADNC cases that were fully staged for all pathologies analyzed and were extremely well matched on age and Braak stage.

Neuropathological Evaluation.

Autopsy was performed using a previously described protocol[34]. Briefly, the left hemibrain was fixed in 10% buffered formalin for at least 14 days, then 1 cm coronal sections were evaluated grossly and sections taken for paraffin-embedding. Hematoxylin and eosin (H&E) was performed on 5 μm sections of middle frontal cortex (Brodmann areas 8/9), rostral superior temporal cortex, inferior parietal cortex, hippocampus (CA1-CA4 and dentate gyrus), entorhinal cortex, basal ganglia, midbrain with substantia nigra, pons with locus coeruleus, and cerebellar cortex with dentate nucleus.

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AD and PART pathology.

Neuritic plaques, diffuse plaques, and neurofibrillary tangles (NFT) were identified on either 10 μm 1% thioflavin-S stained sections using ultraviolet illumination and a 440 μm bandpass excitation filter, or with immunohistochemical staining using antibodies to Aβ (Ab69D/E, polyclonal, Edward Koo, 1:1200) and PHF1 tau (Peter Davies, 1:600). CERAD methods were used to estimate neuritic plaque density[30], Thal phases for spread of amyloid pathology[29], and Braak stages for NFT pathology[35]. PART was defined using the preferred published criteria[1] as Braak stages I-IV tau pathology with Thal phases 0–2 amyloid. Early stage ADNC was also defined as Braak I-IV tau pathology but with Thal phase 3–5 amyloid.

LATE-NC and Vascular pathology.

TDP-43 pathology was identified by immunohistochemistry for total TDP-43 (Proteintech#10782–2-AP polyclonal, 1:12,000) and staged according to LATE-NC consensus guidelines[20] into “amygdala”, “hippocampal”, or “neocortical” stages. Hippocampal sclerosis (HS) was diagnosed independent of TDP-43 pathology by CA1/subiculum neuronal loss out of proportion to hippocampal tau pathology. Vascular pathology assessment included gross and microscopic examination for large and lacunar infarcts, microinfarcts, and gross and microscopic hemorrhages. Arteriolosclerosis, atherosclerosis, and amyloid angiopathy were semi-quantitatively rated as “none”, “mild”, “moderate”, or “severe”.

Clinical and Neuropsychological Evaluation.

Participants had annual standardized clinical, neurological, and neuropsychological evaluations as previously described[36,37]. Clinical evaluation included review of history with the patient and/or informant, mental status testing, and assessment of functional impairment. Clinical Dementia Rating (CDR) score and sum of its six subdomain scores (i.e., CDR sum of boxes) were computed. Neuropsychological assessment included tests for *Global Cognition* (Mini-Mental State Exam (MMSE), Mattis Dementia Rating Scale (DRS)); *Memory* (Visual Reproduction Test, Logical Memory Test, California Verbal Learning Test (CVLT), CERAD Word List); *Language* (30-item Boston Naming Test, Letter Fluency Test (F-A-S),Category Fluency Test); *Executive functions* (modified Wisconsin Card Sorting Test, Trail Making Test Parts A and B, Digit Symbol Substitution Test); and *Visuospatial abilities* (Block Design Test, Visual Reproduction Test copy, Clock Drawing Test).

Consensus clinical diagnoses were made according to published criteria by at least two board-certified neurologists blind to individual cognitive test scores but told whether neuropsychological assessment identified deficits in two or more cognitive domains. Probable or Possible AD or Mild Cognitive Impairment (MCI) was diagnosed according to NINCDS-ADRDA[38] or NIA-AA criteria[39].

Statistical Analyses:

Demographics and prevalence of concomitant pathologies in the PART and ADNC groups were compared using Student’s t-test or Chi-squared test, as appropriate. The odds ratio of a dementia diagnosis at final visit was examined using logistic regression with terms for all four pathologic factors (i.e. PART vs ADNC group for degree of amyloid pathology; Braak

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I-II vs III-IV for degree of tau pathology; LATE-NC− vs LATE-NC+ for presence of TDP43 pathology; Vasc− vs Vasc+ for presence of ischemic vascular pathology), adjusted for age at death, sex, education, and interval from last visit to autopsy. The proportion of all dementia diagnoses attributable to each pathologic factor within our sample was calculated using a previously described method for estimating attributable risk.[40]

Cognitive domain scores were created from the neuropsychological test battery using previously described methods[41,42]. Principal component analysis with varimax rotation identified 4 orthogonal components conceptually labeled as “Visuospatial”, “Memory”, “Executive”, and “Language”. Component scores were derived and transformed to z-scores using reference values from an independent pool of 497 “robust” controls (without pathologic confirmation) diagnosed as cognitively normal on their first and all subsequent annual evaluations (average 5.2±5.0 evaluations).

Cross-sectional analyses of the pathologic predictors of scores on global cognitive measures (MMSE, DRS, and CDR-sob) at the last clinical evaluation were performed using linear regression adjusting for age at death, sex, education, and interval from last evaluation to autopsy. A term for group (PART vs ADNC, i.e. Thal 0–2 vs 3–5) was included in the base model to examine the effect of amyloid on impairment. Next, terms for tau (Braak I-II vs Braak III-IV), TDP-43 (LATE-NC− vs LATE-NC+), or vascular (Vasc− vs Vasc+) pathology were separately added to the model to examine their effects on impairment. An interaction between group and each of the other pathologic measures was tested to examine if these pathologies have differential effects in PART and ADNC but was dropped if it did not reach statistical significance.

Longitudinal decline on each cognitive measure was examined in the 5-year period prior to death using linear mixed effects models adjusting for age at death, sex, education, score at the final visit, and interval from last visit to autopsy, along with each of their interactions by time. Participant-specific intercepts and slopes that were assumed to follow a normal distribution with unknown variance were included as random effects. Much like the cross-sectional models, terms for group (PART vs ADNC) and its interaction with time were included in the base model to examine the effect of amyloid on decline. Next, terms for tau (Braak I-II vs Braak III-IV), TDP-43 (LATE-NC− vs LATE-NC+), or vascular (Vasc− vs Vasc+) pathology were separately added to the model and allowed to interact with time to examine their effects on decline. An interaction between group and each of these pathologic terms on the slope of decline was tested but dropped from the final model if found to not reach significance.

Results:

PART and ADNC Pathology and Clinical Characteristics.

As expected, the ADNC group had higher CERAD neuritic plaque density scores than the PART group ($p=6.8\times10^{-18}$) and the two groups had comparable Braak staging (Figure 1A, p=0.99) with approximately 65% of both groups at Braak stages I-II and 35% at stages III-IV (see Table 1). PART and ADNC groups did not differ in age at death (p=0.44), sex (43–46% female) (p=0.93), age at final clinical evaluation (p=0.24), years of formal

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education (p=0.40), or premorbid verbal IQ measured by the ANART (p=0.21). Both groups had mild impairment (e.g., MMSE 24–25), on average, at last clinical evaluation, and were similar in the proportions of individuals clinically classified as cognitively normal, MCI, or dementia (p=0.39), with approximately 50 to 60 percent of both groups diagnosed with dementia. The APOE ε4 allele was more common in the ADNC group than in the PART group (p=0.01).

LATE-NC and Vascular Co-pathology.

Approximately 24% of individuals in both the PART and ADNC groups had some degree of LATE co-pathology and distributions of LATE-NC stages did not differ between groups (p=0.35) (see Table 1). 77% of both groups had no LATE-NC (Figure 1B, p=0.99). Hippocampal sclerosis was equally common in PART and ADNC at 16–19% of each group (p=0.88). However, in both unadjusted chi-squared analyses and models adjusted for age and sex, LATE pathology was associated with higher Braak stages across both PART and ADNC groups (Figure 1C, p=0.01).

Amyloid angiopathy, which is associated with greater parenchymal amyloid plaques, was more common in ADNC (65%) than in PART (30%) (p=0.004). However, the PART and ADNC groups did not differ in the prevalence or stage of other individual vascular pathologies including atherosclerosis of the circle of Willis, arteriolosclerosis, large or lacunar infarcts, microinfarcts, hemorrhages, or microbleeds. ADNC and PART did not differ in distribution of the number of ischemic vascular pathologies per individual (0–2) tallied across infarcts, microinfarcts, and hemorrhages (Figure 1D, p=0.21). Number of vascular pathologies did not differ between Braak I-II versus Braak III-IV across PART and ADNC groups (Figure 1E, p=0.30), nor in those with versus without concomitant LATE pathology (Figure 1F, p=0.55).

Characteristics by Presence of LATE-NC.

Demographic and pathologic factors were compared in participants with or without LATE-NC (Table 2). The groups were well matched on age (p=0.99) and did not differ in their amyloid staging by CERAD scores (p=0.16) or Thal phasing (p=0.42), nor any of the measures of vascular pathology (p>0.05). However, those with LATE-NC were more likely than those without LATE-NC to have a higher Braak stage (p=0.007). In addition, 55% of the LATE-NC+ group had concomitant hippocampal sclerosis compared to only 7% of the LATE-NC− group (consistent with the well-established association).[20]

Influence of Pathology on Clinical Diagnosis.

In a logistic regression model adjusted for age, sex, and education, and all four pathologic factors, the likelihood of receiving a dementia diagnosis at the clinical evaluation closest to death was the same for those with PART or ADNC (OR 1.25 [95%CI: 0.49–3.24], p=0.65, Figure 2A) (see Table 3). In contrast, those at Braak stage III-IV had a greater likelihood of dementia than those at Braak stage I-II (OR 4.37 [95%CI: 1.52 – 13.53], p=0.007, Figure 2B). Similarly, individuals with concomitant LATE-NC were more likely to receive a dementia diagnosis than those without LATE-NC (OR 4.76 [99%CI: 1.46 – 17.96], p=0.01, Figure 2C). This was not true for those with or without concomitant vascular pathology (OR

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0.86 [95%CI: 0.29 – 2.45], p=0.77, Figure 2D). When tested, interaction terms between each pathologic factor and group were not significant, suggesting that these effects are consistent across PART and ADNC.

Using this logistic regression, the risk of a dementia diagnosis attributable to each pathologic variable in this sample was calculated by comparing the known number of dementia diagnoses to the simulated number of dementia diagnoses if that pathology was absent from all participants (i.e., the pathologic term set to 0 in the model). Results estimated that 21% of the dementia prevalence in the cohort could be attributed to higher Braak stages and 14% to concomitant LATE-NC. When tested, the interaction of LATE-NC and Braak stage was not significant (p=0.11) suggesting that the two pathologies contribute independently to probability of dementia diagnosis.

Overall, individuals receiving a diagnosis of dementia were more likely than those classified with normal cognition or MCI to have some combination of higher Braak stage, LATE-NC, or vascular pathology (Figure 2F). Nearly 80% of those receiving a diagnosis of dementia had at least one of these pathologic features, whereas this was true for less than 50% of those classified with normal cognition or MCI. Of those with normal cognition or MCI, more than half of those with at least one pathology had only vascular pathology.

Influence of Pathology on Cognitive Test Performance.

In models adjusting for age, sex, education, and interval from last evaluation to death, PART and ADNC groups did not differ on MMSE (p=0.61), DRS (p=0.78), or CDR-sob (p=0.40) scores closest to the time of death (within 1.2 ± 1.4 and 0.9 ± 1.1 years for PART and ADNC groups, respectively), nor on domain-specific composite scores for Memory (p=0.96), Executive function (p=0.90), Visuospatial ability (p=0.49), or Language (p=0.21) (see Table 3). Scores achieved on each of these measures are presented as a function of group (PART vs. ADNC) and each of the various pathologies (Braak stage, LATE-NC, vascular) in Figure 3. There were no significant interactions between Group (PART vs. ADNC) and Braak stage, presence of LATE-NC, or presence of vascular pathology in determining global and domain specific-cognitive scores, indicating comparable effects of these pathologies on cognition in PART and ADNC. Collapsing across groups, individuals at Braak stage III-IV scored worse than those at Braak stage I-II by 4.4 MMSE points (95% CI: 1.8–7.0), 10.8 DRS points (95% CI: 1.1–20.5), 6.9 CDR-sob points (95% CI: 4.6–9.1), and 0.9 standard deviations (SDs) on the Memory composite (95% CI: 0.2–1.6). Patients with concomitant LATE-NC were more impaired by 5.8 MMSE points (95% CI: 3.0–8.6), 17.5 DRS points (95% CI: 7.1–27.9), 5.2 CDR-sob points (95% CI: 2.1–8.2), 0.8 SDs on a Memory composite (95% CI: 0.1–1.6), and 1.1 SDs on a Language composite (95% CI: 0.2–2.0). Those with concomitant vascular pathology performed worse by 10.2 DRS points (95% CI: 0.1–20.3) and 1.3 SDs on an Executive composite (95% CI: 0.3–2.3).

Influence of Pathology on Rate of Cognitive Decline.

PART and ADNC groups did not differ in rates of decline in the 5-year period prior to death on the MMSE, DRS, CDR-sob, or any cognitive composite measure (see Figure 4 and Table 4). After collapsing across PART and ADNC, individuals at Braak stage III-IV declined 1.3

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points/year more rapidly on the MMSE (95% CI: 0.3–2.4), 2.8 points/year more rapidly on CDR-sob (95% CI: 1.5–4.2), and 0.4 standard deviations (SDs) per year more rapidly on the Memory composite score (95% CI: 0.1–0.7) than those at Braak stage I-II. Similarly, individuals with concomitant LATE-NC pathology declined 1.9 points/year more rapidly on the MMSE (95% CI: 0.8–3.0), 7.76 points/year more rapidly on the DRS (95% CI: 3.4–12.7), 1.93 points/year more rapidly on CDR-sob (95% CI: 0.4–3.7), and 0.48 SD/year more rapidly on the Language composite score (95% CI: 0.1–0.8) than those without concomitant LATE-NC. Individuals with concomitant vascular pathology declined 5.18 points/year more rapidly on the DRS (95% CI: 0.6–10.2) than those without vascular co-pathology. There were no significant interactions between group and Braak stage, presence of LATE-NC, or presence of vascular pathology on rates of decline on any cognitive measure.

Discussion:

The present study examined the contributions of concomitant LATE-NC or ischemic vascular neuropathology to the clinical and cognitive deficits associated with tangle pathology restricted to the medial temporal lobe (i.e., Braak I-IV) in the absence (i.e., PART) or presence (i.e., ADNC) of significant amyloid plaques. Our study showed no difference in the prevalence of concomitant LATE-NC pathology (about 24% in each condition) or cerebrovascular pathology (about 25–30% in each condition) in PART and early-stage ADNC. Only cerebral amyloid angiopathy (CAA) occurred more often in ADNC than in PART, in concert with a higher APOE ε4 allele prevalence. There was little difference in the clinical presentations of PART and early-stage ADNC. The groups did not differ in severity of global cognitive impairment or impairment in specific cognitive domains at the last evaluation before death, nor in the proportion of individuals who received a final clinical diagnosis of dementia (50–60% in each group) or MCI (10–25% of each group). Rate of decline in global cognition or specific cognitive domains also did not differ in PART and ADNC.

The presence of concomitant LATE-NC was associated with worse global cognition, worse memory impairment, and a faster rate of decline in language abilities across both PART and ADNC. The effects of LATE-NC on cognition were similar in both groups (i.e., there was no group by LATE-NC interaction effect), and none of the participants with LATE-NC had any clinical features of FTD or neuropathologic features of FTLD. The primary impact of LATE-NC on memory and language is consistent with the predominance of TDP-43 pathology in limbic regions important for these cognitive functions, and is largely consistent with reported effects of LATE-NC in other contexts such as advanced AD and hippocampal sclerosis[21,43,44]. These findings suggest that undetected LATE-NC may have influenced the severity and nature of cognitive decline reported in previous studies of PART where cognitive decline seemed out of proportion to the degree of tangle pathology[1,6,10–12,24].

Concomitant vascular pathology in the form of infarcts, microinfarcts, and hemorrhages was associated with greater executive function deficits in both PART and ADNC. This finding is consistent with a recent multi-center cohort analysis which showed that vascular pathology and age are the strongest predictors of cognitive impairment in patients with PART - beyond degree of tau pathology[11]. While vascular pathology is a well-known predictor of cognitive

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impairment, wide variability in the location and extent of associated necrosis makes it difficult to consistently characterize its effects on cognition. The most commonly reported deficit is executive dysfunction attributable to diffuse white matter disruption[45]. In line with this view, the greatest impact of concomitant vascular co-pathology in PART and ADNC in the present study was on executive functions. We also found that degree of executive dysfunction, rather than its rate of decline, was impacted by concomitant vascular pathology in PART and ADNC. This finding is consistent with an expected step-wise progression of vascular pathology and its impact on cognition. Cerebral amyloid angiopathy was more prevalent in ADNC than in PART, consistent with its known association with amyloid plaque deposition, but the impact of CAA on cognition is marginal[46,47] and not likely to contribute to differences in the clinical presentation of ADNC and PART. Overall, we found no difference in the influence of concomitant cerebrovascular pathology on clinical presentation or cognitive decline in PART and ADNC.

Consistent with previous studies[1,9], we found that higher Braak stage (i.e., III-IV vs. I-II) was associated with greater memory impairment, worse global cognition (based on tests weighted towards memory function), and faster memory and global cognitive decline in PART and early-stage ADNC. Furthermore, Braak stage influenced memory and its decline in PART and ADNC to a similar degree (i.e., there was no group by interaction effect). The specificity of effects on memory is not surprising given that, by definition, tau pathology in PART and early-stage ADNC is restricted to medial temporal lobe structures critical for memory. The association we find between cognition and Braak stage in PART and AD may explain why previous studies that compared PART with little or no neocortical tau pathology (Braak I-IV) to late stage AD with significant neocortical tau pathology (Braak V-VI) found greater cognitive impairment and faster cognitive decline in AD than in PART[6,8,13]. When patients with PART or ADNC with nearly identical age, sex, and Braak stage were compared in the present study, no important differences in cognition were found. A previous study using data from the National Alzheimer's Coordinating Center (NACC) found small and inconsistent differences in cognition between definite PART (i.e., Braak III-IV) and AD restricted to Braak III-IV, but did not take into account the potential presence and influence of LATE-NC or cerebrovascular co-pathologies[10].

Similarities in cognitive outcomes of patients with PART or ADNC who differed only in the presence or absence of significant amyloid pathology (i.e., PART: Thal phase 0–2; ADNC: Thal phase 3–5) is consistent with previous findings of a minimal direct effect of amyloid deposition on cognition in AD[48]. Current conceptualizations of AD suggest, however, that amyloid deposition may accelerate neurofibrillary tangle formation and neuron loss that correlates with cognitive decline[49]. Thus, memory decline might be expected to be faster in ADNC than in PART. This was not the case in the present study. We found no differences in rates of memory or other cognitive decline for PART and ADNC at any Braak stage (even accounting for cerebrovascular and LATE-NC co-pathology). It should be noted that this conclusion is limited by the modest sample size of the study and the inherent nature of autopsy-based studies which only allow rate of pathology accumulation to be inferred. While we adjust our analyses for the test-autopsy interval, this may not always capture the complexity of multiple co-pathologies that may progress at different rates. This question may be more clearly addressed in future longitudinal studies of PART and low level ADNC

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using tau and amyloid PET imaging, although such studies will be limited by the inability to account for concomitant pathologies (e.g., Lewy bodies, LATE-NC).

Concomitant LATE-NC (presence vs. absence) and higher Braak stages (Braak III-IV vs. Braak I-II) were associated with similar increases in likelihood of dementia at the last clinical evaluation before death in both PART and ADNC, each accounted for 15–20% of dementia diagnoses, and they had comparable magnitudes of effects on global cognitive decline. This suggests that LATE-NC may have as great an impact as degree of tau pathology on cognitive decline and development of dementia in PART and early-stage ADNC, and is consistent with studies showing that both tau and LATE-NC are major predictors of degree of medial temporal lobe atrophy on MRI in patients with PART or ADNC[50]. IGiven our results, it may be that a substantial portion of the cognitive impairment and cognitive decline attributed to PART in previous studies with nearly identical inclusion criteria to ours[1,10,11] could be due to unassessed LATE-NC.

A limitation of the present study is that there were changes in clinical and neuropathologic practices and criteria over the 35 years during which this clinical-pathological cohort was established. We minimized potential bias this may have caused by conducting immunohistochemical staining for TDP-43 and amyloid on all participants in order to retrospectively apply current consensus neuropathological criteria for AD and LATE-NC. Additionally, the extent of tau pathology in both PART and AD was approximated using the Braak staging scheme that was designed for use in AD. As PART is relatively recently defined, it is possible that Braak staging is not directly applicable to PART. Some studies have circumvented this concern by assessing p-tau staining density[11]. However, a previous study has shown that the distribution of tau pathology is largely consistent between early AD and PART, suggesting that Braak stage is a sufficient proxy for the extent of tau pathology in both conditions[13]. Lastly, this study was based on a convenience sample of cases from an ADRC brain that is biased towards Caucasians and those with high levels of education, and away from those with other significant medical comorbidities that may have excluded them from participation in the longitudinal ADRC study. This limits the generalizability of these results to the general population, and in particular the generalizability of attributable risk calculations which are traditionally more meaningful in the context of epidemiologic studies.

Despite these limitations, our findings have important clinical implications. We demonstrate here that LATE-NC contributes to cognitive decline in the context of mild NFT and amyloid plaque pathology. The contributions of undetected LATE-NC to risk of cognitive impairment and dementia in individuals with PART or early-stage ADNC may increase variability in the prognostic value of *in vivo* tau and amyloid PET imaging or CSF and plasma biomarkers. In addition, undetected LATE-NC \ could dampen therapeutic benefits observed of anti-amyloid or anti-tau medications in clinical trials that include patients with early stage tauopathy or AD. Finally, our findings strongly highlight the need to further investigate mechanisms underlying TDP-43 proteinopathies and to develop biomarkers and treatments specific for LATE-NC.

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Abbreviations:

PART	Primary Age-related Tauopathy
ADNC	Alzheimer's Disease Neuropathologic Change
LATE-NC	Limbic Age-related TDP-43 Encephalopathy Neuropathologic Change
MMSE	Mini Mental State Exam
DRS	(Mattis) Dementia Rating Scale
CDR-sob	Clinical Dementia Rating, sum of boxes scale

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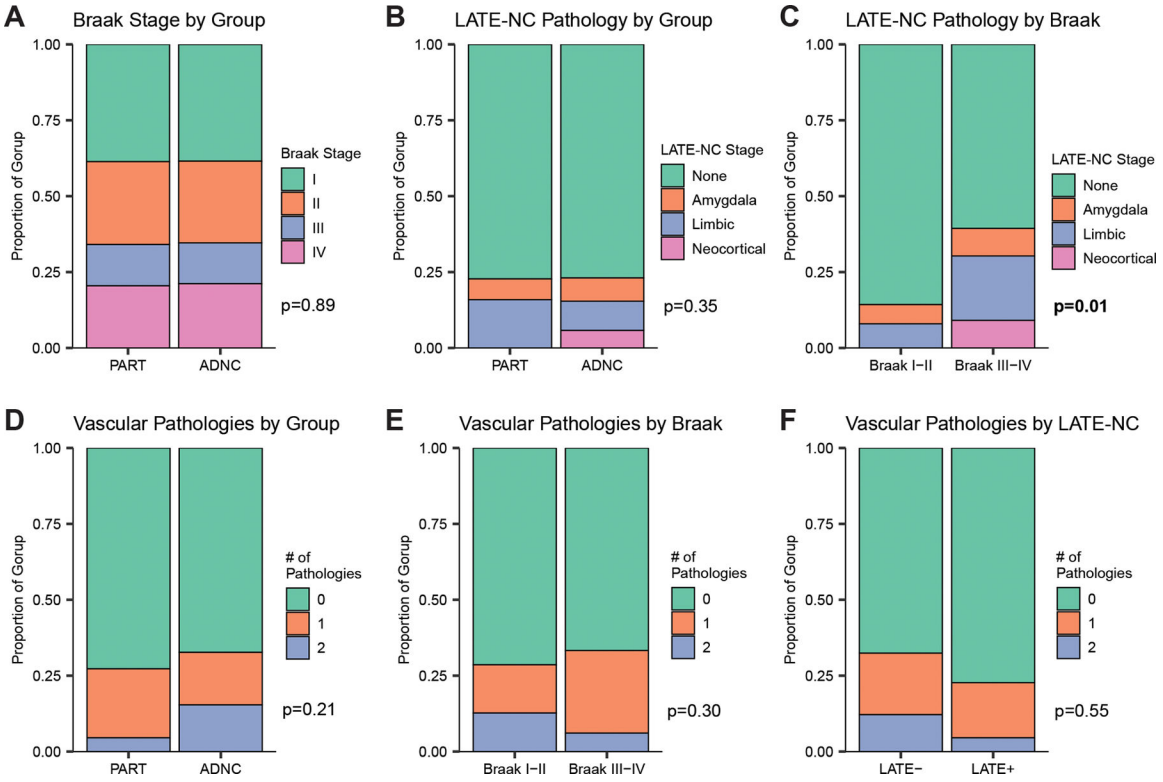

Figure 1: Comparative distributions of pathologies.

The distribution of Braak stages (A) and stages of concomitant LATE-NC pathology (B) did not differ between participants with PART and ADNC in our sample. However, those with relatively higher Braak stages (i.e. III-IV vs I-II) were more likely to have concomitant LATE-NC pathology (C), even in models adjusted for age and sex. In contrast, the number of concomitant ischemic vascular pathologies (tallied across infarcts, microinfarcts, and hemorrhages/microbleeds) did not differ between PART and ADNC (D), Braak stages (E), or presence of LATE-NC co-pathology (F).

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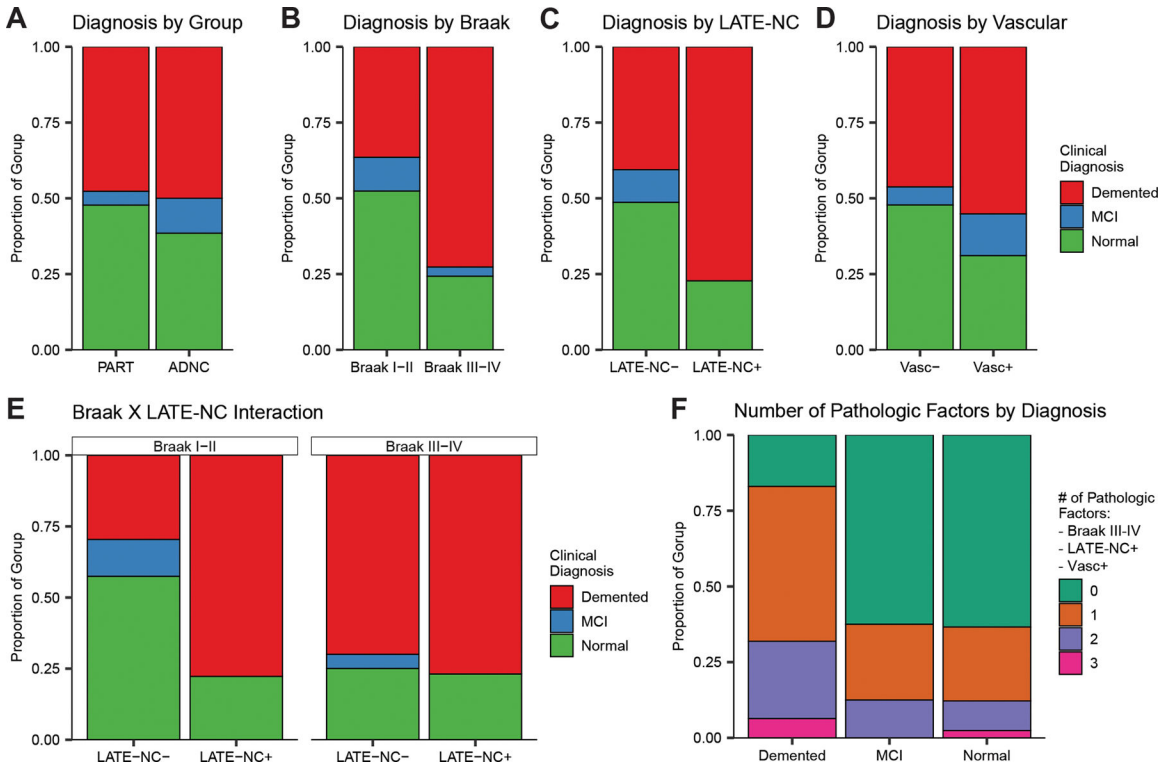

Figure 2: Clinical diagnoses of participants at the evaluation closest to autopsy by pathology.

The distributions of clinical diagnoses at the clinical evaluation closest to death presented in the participants divided by each of the four pathologic factors (A-D) suggests while there was no significant difference between individuals with PART vs ADNC and between those with vs without vascular pathology, individuals with higher Braak stages or concomitant LATE-NC were more likely to be demented prior to death. Since concomitant LATE-NC pathology is more likely among those with higher Braak stages (Figure 1C), we examined the interaction of those pathologies with regards to the diagnosis (D) and observed that either higher Braak stages, concomitant LATE-NC, or both appear to increase the likelihood of a dementia diagnosis compared to those with neither pathology. If the number of significant pathologic factors (tallied across higher Braak, concomitant LATE-NC, and concomitant Vascular) are examined by the final clinical diagnosis (F), we can see that those with dementia were far more likely (>75%) to have at least one of these pathologies compared to those with either MCI or Normal cognition (<50%).

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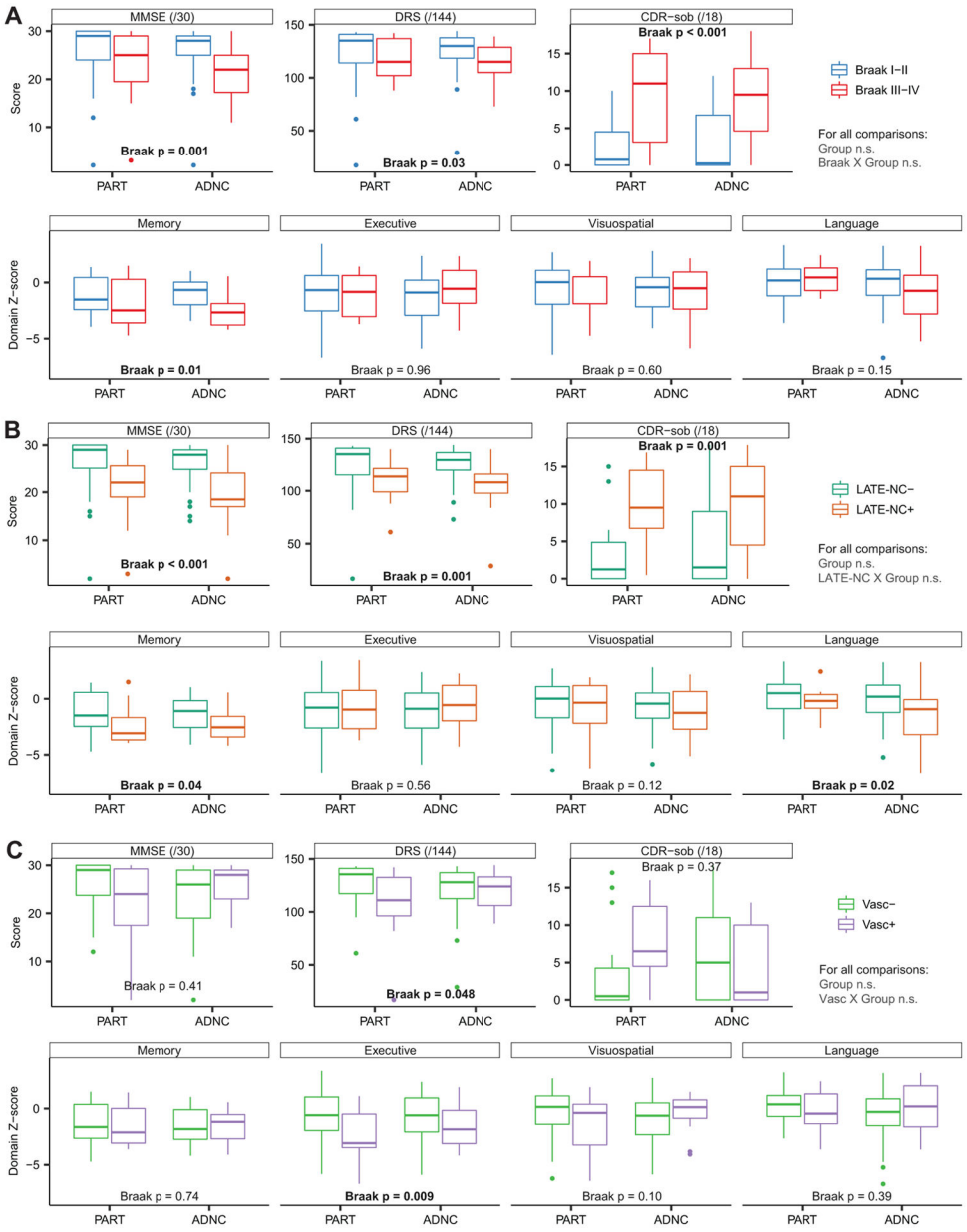

Figure 3: Cognitive performance at the evaluation closest to autopsy by pathologic factor

Cognitive performance of the participants at the evaluation closest to death is presented as a function of higher Braak stage (A), concomitant LATE-NC pathology (B), or concomitant vascular pathology (C) divided by group (i.e. PART vs ADNC). There were no significant differences in performance between PART and ADNC on any measures, and no significant interactions of the group term with each of the three other pathologic factors, suggesting that they produce similar effects on cognition across the groups. However, those with higher Braak stages performed worse on each of the three global cognitive measures (MMSE, DRS, CDR-sob), as well as the Memory cognitive composite. Similarly, those with concomitant LATE-NC pathology performed worse on the three global measures and

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both the Memory and Language composites. Those with concomitant vascular pathology declined more rapidly on the DRS. For effect sizes and p value please see Table 4.

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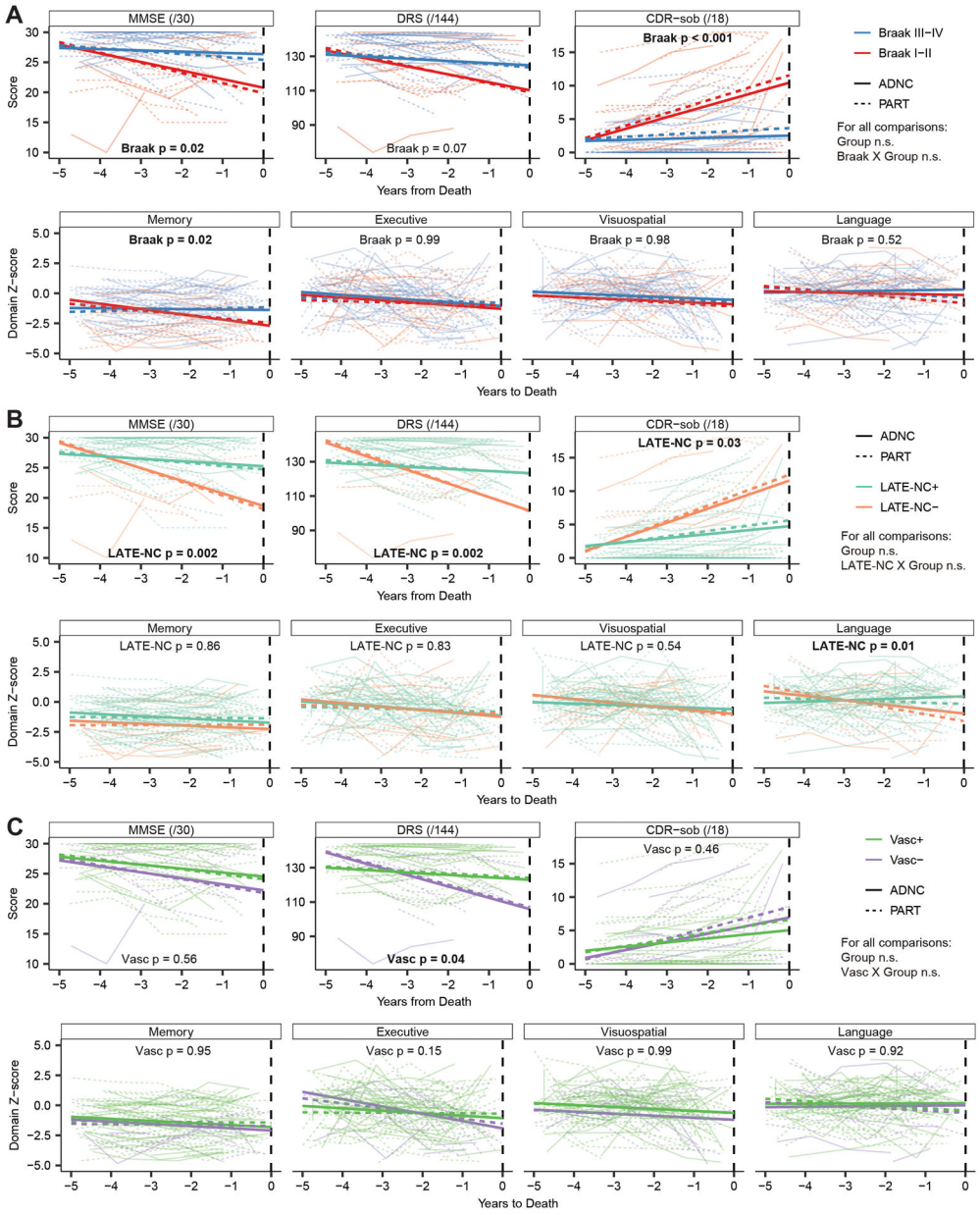

Figure 4: Rates of longitudinal cognitive decline prior to autopsy by pathologic factor

Trajectories of cognitive decline in the 5 years prior to autopsy of the participants are presented as a function of higher Braak stage (A), concomitant LATE-NC pathology (B), or concomitant vascular pathology (C) divided by group (i.e. PART vs ADNC). There were no significant differences in performance between PART and ADNC on any measures, and no significant interactions of the group term with each of the three other pathologic factors, suggesting that they produce similar effects on cognitive delcine across the groups. However, those with higher Braak stages declined more rapidly on the MMSE, CDR-sob, and the Memory composite. Similarly, those with concomitant LATE-NC pathology performed

worse on all three global measures and the Language composite. Those with concomitant vascular pathology performed worse on the DRS and the Executive composite.

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Table 1:

Participant Characteristics

	PART (N=44)	ADNC (N=52)	P value
Age at Death (y)	88.0 ± 7.4	89.1 ± 6.2	0.44
Age at Final Visit	86.7 ± 7.3	88.4 ± 6.4	0.24
Final Visit – Autopsy Interval	1.2 ± 1.4	0.9 ± 1.1	0.27
Female	19 (43%)	24 (46%)	0.93
Thal Phase: 0 (A0) / 1–2 (A1) / 3 (A2) / 4–5 (A3)	20 / 24 / 0 / 0 (45% / 55% / 0% / 0%)	0 / 0 / 13 / 39 (0% / 0% / 25% / 75%)	(definition)
Braak Stage: I-II (B1) / III-IV (B2) / V-VI (B3)	29 / 15 / 0 (66% / 34% / 0%)	34 / 18 / 0 (65% / 35% / 0%)	0.99
Neuritic Plaques: None (C0) / Sparse (C1) / Moderate (C2) / Frequent (C3)	39 / 5 / 0 / 0 (89% / 11% / 0% / 0%)	0 / 9 / 38 / 5 (0% / 17% / 73% / 10%)	**6.79×10^{-18}**
LATE-NC: None / Amyg / Limbic / Neocortical	34 / 3/ 7/ 0 (77% / 7% / 16% / 0%)	40 / 4 / 5 / 3 (77%, 8% / 10% / 6%)	0.35
Amyloid Angiopathy: None / Mild / Moderate / Severe	31 / 7 / 5 / 1 (70% / 16% / 11% / 2%)	18 / 13 / 13 / 8 (35% / 25% / 25% / 15%)	**0.004**
Atherosclerosis: None / Mild / Moderate / Severe	8 / 15 / 14 / 6 (18% / 34% / 32% / 14%)	7 /12 / 26 / 7 (13% / 23% / 50% / 13%)	0.35
Arteriolosclerosis: None / Mild / Moderate / Severe	12 / 13 / 16 / 3 (27% / 30% / 36% / 7%)	16 / 18 / 16 / 2 (31% / 35% / 31% / 4%)	0.82
Infarcts	8 (18%)	12 (23%)	0.74
Microinfarcts	4 (9%)	10 (19%)	0.27
Hemorrhage/Microbleeds	2 (5%)	3 (6%)	0.99
Hippocampal Sclerosis	7 (16%)	10 (19%)	0.88

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Table 2:

Participant Characteristics by LATE-NC

	LATE-NC − (N=74)	LATE-NC + (N=22)	P value
Age at Death (y)	88.4 ± 6.8	89.0 ± 6.9	0.73
Age at Final Visit	87.6 ± 6.9	87.6 ± 6.9	0.99
Final Visit – Autopsy Interval	0.8 ± 0.8	1.3 ± 1.8	0.72
Female	35 (47%)	8 (36%)	0.51
Thal Phase: 0 (A0) / 1–2 (A1) / 3 (A2) / 4–5 (A3)	15 / 19 / 11 / 29 (20% / 26% / 15% / 39%)	5 / 5 / 2 / 10 (23% / 23% / 9% / 45%)	0.42
Braak Stage: I-II (B1) / III-IV (B2) / V-VI (B3)	54 / 20 / 0 (73% / 27% / 0%)	9 / 13 / 0 (41% / 59% / 0%)	**0.007**
Neuritic Plaques: None (C0) / Sparse (C1) / Moderate (C2) / Frequent (C3)	29 / 11 / 32 / 2 (39% / 15% / 43% / 3%)	10 / 3 / 6 / 3 (45% / 14% / 27% / 14%)	0.16
LATE-NC: None / Amyg / Limbic / Neocortical	74 / 0 / 0 / 0 (100% / 0% / 0% / 0%)	0 / 7 / 12 / 3 (0%, 32% / 55% / 14%)	(definition)
Amyloid Angiopathy: None / Mild / Moderate / Severe	42 / 12 / 12 / 8 (57% / 16% / 16% / 11%)	7 / 8 / 6 / 1 (32% / 36% / 27% / 5%)	0.07
Atherosclerosis: None / Mild / Moderate / Severe	10 / 18 / 35 / 11 (14% / 24% / 47% / 15%)	7 /6 / 9 / 0 (32% / 27% / 41% / 0%)	0.14
Arteriolosclerosis: None / Mild / Moderate / Severe	21 / 25 / 23 / 5 (28% / 34% / 31% / 7%)	7 / 6 / 9 / 0 (32% / 27% / 41% / 0%)	0.52
Infarcts	17 (23%)	3 (14%)	0.52
Microinfarcts	12 (16%)	2 (9%)	0.62
Hemorrhage/Microbleeds	4 (5%)	1 (5%)	0.99
Hippocampal Sclerosis	5 (7%)	12 (55%)	$\mathbf{1.3 \times 10^{-6}}$

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Table 3:

Statistics for cognitive performance at last visit by pathologic feature and their interaction with group

	PART vs ADNC		Braak I-II vs Braak III-IV			LATE-NC− vs LATE-NC +			Vasc− vs Vasc+		
	Coefficient (95% CI)	**Group P value**	**Coefficient (95% CI)**	**Braak P value**	**Group Interaction P value**	**Coefficient (95% CI)**	**LATE P value**	**Group Interaction P value**	**Coefficient (95% CI)**	**Vasc P value**	**Group Interaction P value**
MMSE	−0.67 (−3.25 – 1.91)	0.606	**−4.38 (−7.01 – −1.75)**	**0.001**	0.115	**−5.8 (−8.62 – −2.98)**	**<0.001**	0.769	−1.20 (−4.08 – 1.67)	0.408	0.053
DRS	−1.33 (−10.56 – 7.91)	0.776	**−10.81 (−20.53 – −1.08)**	**0.03**	0.256	**−17.51 (−27.89 – −7.14)**	**0.001**	0.614	**−10.20 (−20.32 – −0.08)**	**0.048**	0.118
CDR-sob	1.12 (−1.50 – 3.75)	0.396	**6.88 (4.62 – 9.13)**	**<0.001**	0.966	**5.17 (2.10 – 8.24)**	**0.001**	0.737	1.32 (−1.59 – 4.23)	0.369	0.133
Memory	−0.02 (−0.68 – 0.64)	0.956	**−0.90 (−1.60 – −0.21)**	**0.011**	0.173	**−0.82 (−1.59 – −0.05)**	**0.037**	0.858	−0.13 (−0.89 – 0.63)	0.741	0.749
Executive	0.05 (−0.83 – 0.94)	0.904	−0.03 (−0.97 – 0.92)	0.958	0.791	0.28 (−0.76 – 1.32)	0.596	0.445	**−1.30 (−2.27 – −0.34)**	**0.009**	0.117
Visuospatial	−0.34 (−1.30 – 0.62)	0.487	−0.27 (−1.31 – 0.76)	0.600	0.655	−0.89 (−2.02 – 0.24)	0.12	0.65	−0.90 (−1.98 – 0.18)	0.102	0.430
Language	−0.50 (−1.28 – 0.28)	0.205	−0.62 (−1.46 – 0.22)	0.145	0.057	**−1.08 (−2.00 – −0.16)**	**0.021**	0.627	0.39 (−0.51 – 1.29)	0.391	0.153

For each cognitive test or composite, the coefficient (99% Confidence Interval) for the cross-sectional performance at the last visit is provided along with the p value for each pathologic term as indicated along the top. For each pathologic term other than the Group term (i.e., PART vs ADNC), the p value for the interaction of the pathologic term with Group is also provided so assess if the effects differ between those with PART or ADNC.

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Table 4:

Statistics for longitudinal slopes of decline by pathologic feature and their interaction with group

	PART vs ADNC		Braak I-II vs Braak III-IV			LATE-NC− vs LATE-NC +			Vasc− vs Vasc+		
	Coefficient (95% CI)	**Group P value**	**Coefficient (95% CI)**	**Braak P value**	**Group Interaction P value**	**Coefficient (95% CI)**	**LATE P value**	**Group Interaction P value**	**Coefficient (95% CI)**	**Vasc P value**	**Group Interaction P value**
MMSE	−0.16 (−1.11 – 0.79)	0.752	**−1.31 (−2.40 – −0.32)**	**0.019**	0.289	**−1.89 (−3.04 – −0.84)**	**0.002**	0.706	−0.34 (−1.52 – 0.74)	0.562	0.309
DRS	0.12 (−3.77 – 4.08)	0.952	−4.07 (−8.42 – −0.06)	0.066	0.258	**−7.76 (−12.74 – −3.36)**	**0.002**	0.546	**−5.18 (−10.18 – −0.63)**	**0.037**	0.194
CDR-sob	0.61 (−0.81 – 2.08)	0.439	**2.77 (1.47 – 4.18)**	**<0.001**	0.417	**1.93 (0.38 – 3.66)**	**0.029**	0.202	0.55 (−0.75 – 1.91)	0.455	0.838
Memory	0.14 (−0.14 – 0.43)	0.351	**−0.4 (−0.72 – −0.10)**	**0.015**	0.409	0.03 (−0.31 – 0.35)	0.864	0.375	−0.01 (−0.37 – 0.36)	0.951	0.555
Executive	0.15 (−0.25 – 0.56)	0.471	0.00 (−0.44 – 0.45)	0.998	0.619	−0.06 (−0.55 – 0.44)	0.829	0.769	−0.40 (−0.92 – 0.13)	0.151	0.829
Visuospatial	−0.02 (−0.49 – 0.46)	0.952	−0.01 (−0.53 – 0.50)	0.977	0.529	−0.19 (−0.78 – 0.39)	0.540	0.935	0.00 (−0.61 – 0.59)	0.990	0.066
Language	−0.21 (−0.52 – 0.09)	0.194	−0.12 (−0.46 – 0.22)	0.517	0.539	**−0.48 (−0.84 – −0.13)**	**0.013**	0.757	0.02 (−0.39 – 0.41)	0.921	0.742

For each cognitive test or composite, the coefficient (99% Confidence Interval) for the annualized rate of decline is provided along with the p value for each pathologic term as indicated along the top. For each pathologic term other than the Group term (i.e., PART vs ADNC), the p value for the interaction of the pathologic term with Group is also provided so assess if the effects differ between those with PART or ADNC.