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Cognitive and Neuropsychological Profiles in Alzheimer's Disease and Primary Age-Related Tauopathy and the Influence of Comorbid Neuropathologies

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Abstract

Background: Alzheimer's disease neuropathologic change (ADNC) is defined by the progression of both hyperphosphorylated-tau (p-tau) and amyloid-β (Aβ) and is the most common underlying cause of dementia worldwide. Primary age-related tauopathy (PART), an Aβ-negative tauopathy largely confined to the medial temporal lobe, is increasingly being recognized as

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CONFLICTOFINTEREST
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an entity separate from ADNC with diverging clinical, genetic, neuroanatomic, and radiologic profiles.

Objective: The specific clinical correlates of PART are largely unknown; we aimed to identify cognitive and neuropsychological differences between PART, ADNC, and subjects with no tauopathy (NT).

Methods: We compared 2,884 subjects with autopsy-confirmed intermediate-high stage ADNC to 208 subjects with definite PART (Braak stage I–IV, Thal phase 0, CERAD NP score “absent”) and 178 NT subjects from the National Alzheimer’s Coordinating Center dataset.

Results: PART subjects were older than either ADNC or NT patients. The ADNC cohort had more frequent neuropathological comorbidities as well as *APOE*4 ε4 alleles than the PART or NT cohort, and less frequent *APOE*2 ε2 alleles than either group. Clinically, ADNC patients performed significantly worse than NT or PART subjects across cognitive measures, but PART subjects had selective deficits in measures of processing speed, executive function, and visuospatial function, although additional cognitive measures were further impaired in the presence of neuropathologic comorbidities. In isolated cases of PART with Braak stage III-IV, there are additional deficits in measures of language.

Conclusion: Overall, these findings demonstrate underlying cognitive features specifically associated with PART, and reinforce the concept that PART is a distinct entity from ADNC.

Keywords

Alzheimer’s disease; cerebrovascular disease; Clinical Dementia Rating; Lewy body dementia; limbic-predominant age-related TDP-43 encephalopathy neuropathologic change (LATE-NC); Mini-Mental State Examination; primary age-related tauopathy

INTRODUCTION

Alzheimer’s disease (AD) was first described microscopically in the early 20th century and is the most common cause of dementia worldwide [1, 2]. Alzheimer’s disease neuropathologic change (ADNC) is defined by the presence of hyperphosphorylated-tau (p-tau) neurofibrillary degeneration, a process which typically proceeds from medial temporal lobe structures into the neocortex in well-defined Braak stages [3], amyloid-β plaques (Aβ), which proceed from the neocortex to brainstem and cerebellum in Thal phases [4], and neuritic plaques (NP) in the neocortex [5]. These features, in particular Braak stage, correlate with cognitive status [5, 6], although there is growing evidence that some of the cognitive effects associated with this disorder are due, at least in part, to coexisting neuropathologic disorders, most commonly including limbic-predominant age-related TDP-43 encephalopathy neuropathologic change (LATE-NC), Lewy body disease (LBD), and cerebrovascular disease (CVD) [7–19].

Primary age-related tauopathy (PART) is thought to be an Aβ-independent tauopathy that is primarily restricted to the medial temporal lobe, corresponding roughly from Braak stages I–IV in the absence of significant Aβ-deposition [20–24]. “Definite” PART is currently defined as Braak stage I–IV in the complete absence of Aβ (Thal phase 0 and CERAD NP score “absent”), while “possible” PART is defined as Braak stage I–IV with minimal Aβ deposition (Thal phase 1–2 and/or CERAD NP score "sparse") [20, 22]. Neurofibrillary degeneration in PART is thought to affect the CA2 hippocampal subregion early in the disease course, while in ADNC the entorhinal cortex and CA1 subregion are more severely affected with relative CA2 sparing [22, 24–26]. Numerous studies have also shown that PART subjects differ from subjects with ADNC in terms of *APOE* ε2 and ε4 allele frequency [27–31], *MAPT* haplotype [32], imaging characterization of brain atrophy patterns [33, 34], and clinical/cognitive features [27, 31, 35–39]. Clinically, PART patients have been shown to have relative preservation of attention, memory, language, and visuospatial function until later in the disease course, as well as a slower rate of cognitive decline after initial symptom onset compared to patients with autopsy-proven ADNC. We and others have demonstrated that cognitive function in subjects with PART is not significantly correlated with Braak stage, but rather the presence of hippocampal atrophy, white matter pathology, cerebrovascular disease, aging-related tau astrogliopathy (ARTAG), the presence and severity of LATE-NC, and the overall hippocampal tau burden [22, 27, 40, 41], the latter of which is an observation confirming imaging studies suggesting an inverse correlation between medial temporal lobe tau levels, measured with positron emission tomography (PET), and cognitive performance [42]. Still, there remains debate as to whether PART is a distinct neuropathologic entity or belongs to the early stage of the ADNC spectrum [43–45].

In this study, we leverage the National Alzheimer's Coordinating Center database to compare demographics, genetics, neuropathologic features (including an array of comorbid disease states), cognitive features, and neuropsychological findings in autopsy-confirmed definite PART (n = 208), ADNC (n = 2,884), and "no tauopathy" (NT) (n = 178). We demonstrate significant differences in these profiles with and without neuropathologic comorbidities, suggesting that PART has a subtle but identifiable clinical correlate, with significant differences from ADNC.

METHODS

Case selection and exclusion criteria

For this study, we used the Uniform Data Set (UDS) and Neuropathology (NP) data set from the National Alzheimer's Coordinating Center (NACC), established with funding from the National Institute on Aging (U01 AG016976). UDS and NP data were downloaded from NACC (https://naccdata.org/). Standardized UDS variable definitions [46] and NP variable definitions [47] from NACC were used, as described previously [48, 49]. A total of 7,709 unique NACC cases with last patient encounter within the final 24 months of life were identified [19]. In total, 3,803 cases were excluded for not having sufficient data to determine ADNC level. Of the remaining 3,906 cases, we then excluded 111 cases with progressive supranuclear palsy (NACCPROG), 72 cases with corticobasal degeneration (NACCCBD), 43 cases with Pick's disease (NACCPICK), 4 cases with *MAPT* mutation (NPFTDT2), 184 cases with other, unspecified frontotemporal dementia (FTD)-Tau (NPFTDTAU), 70 cases with FTD-TDP (NPFTDTDP), 12 cases with chronic traumatic encephalopathy (CTE) (NPFTDT7), 87 cases with prion disease (NACCPRIO), 40 cases with amyotrophic lateral sclerosis/motor neuron disease (NPALSMND), 6 cases with Down syndrome (NACCDOWN), 5 cases with multiple system atrophy (NPPDXB), and 2 cases with trinucleotide repeat diseases (NPPDXD). Of note, a number of cases had multiple exclusionary criteria. Of the 3,270 cases remaining, 2,884 cases had intermediate or high level ADNC [5], 208 had definite PART [20, 22], and 178 had no identified tauopathy (Supplementary Figure 1). Demographic data on all individuals included in these three groups can be found in Table 1.

Neuropathologic variables

ADNC level was determined from the NACC variable NPADNC. In cases where NPADNC was not available but other sufficient data were available to determine ADNC, ADNC levels were derived from a combination of Braak stage (NACCBRAA), Thal phase (NPTHAL), and CERAD neuritic plaque (NP) score (NACCNEUR) [5, 50]. LATE-NC stage was assessed using NACC variables NPTDPB (TDP-43 immunoreactive inclusions in amygdala), NPTDPC (TDP-43 immunoreactive inclusions in hippocampus), NPTDPD (TDP-43 immunoreactive inclusions in entorhinal/inferior temporal cortex), and NPTDPE (TDP-43 immunoreactive inclusions in neocortex). Cases were assigned LATE-NC stage 0 in the absence of TDP-43 immunoreactivity in any region, LATE-NC stage 1 with TDP-43 immunoreactive inclusions in the amygdala and/or entorhinal cortex, LATE-NC stage 2 with TDP-43 immunoreactive inclusions in the amygdala and hippocampus proper, and LATE-NC stage 3 with TDP-43 inclusions in the amygdala, hippocampus, and neocortex [51–53]. Lewy body pathology was assessed using the NACC variable NACCLEWY, where absence of Lewy bodies represents stage 0, brainstem predominant is stage 1, limbic is stage 2, and diffuse neocortical is stage 3, as previously described [54–56]. Cerebrovascular disease was assessed using the presence of infarcts/lacunes (NACCINF), single or multiple old hemorrhages (NPHEMO), white matter rarefaction (NPWMR), and moderate to severe arteriolosclerosis (NACCARTE), also as previously described [19, 57–61].

Cognitive and neuropsychological variables

Representative cognitive and neuropsychological variables encompassing overall cognition, including global Clinical Dementia Rating (CDR; CDR-GLOB), CDR Sum of Boxes (CDRSUM), and Mini-Mental State Examination (MMSE; NAC-CMMSE) and more specific cognitive domains including attention, processing speed, executive function, memory, and language (including both verbal fluency and naming) were assessed as previously described [27, 38, 62, 63]. Memory testing consisted of logical memory (LOGIMEM) and logical memory recall (MEMUNITS), attention testing consisted of digit span forward (DIGIF) and digit span backward (DIGIB), processing speed testing consisted of Trail Making Test Part A (TMT-A; TRAILA) and Wechsler Adult Intelligence Scale (WAIS) Digit Symbol Substitution Test (WAIS DS; WAIS), executive function was represented by Trail Making Test Part B (TMT-B; TRAILB), and language was represented by animal list generation/animal fluency (ANIMALS), vegetable list generation/vegetable fluency (VEG), and Boston Naming Test, 30 odd items (BNT; BOSTON).

Data analysis

All statistical analyses were performed with GraphPad Prism version 9 (GraphPad Software, Inc., La Jolla, CA, USA). All cognitive/neuropsychiatric variables were adjusted by age, sex, and education levels, and z-scores were produced from these data using established coefficients and formulas previously described in detail and adjusted by age, sex, and education level [64–66]. Differences between age, education, CDR, CDR sum of boxes, MMSE, and all neuropsychological variables between groups (NT, PART, and ADNC) were evaluated using multiple *t*-tests. Proportion of cases with gender, race, *APOE* status, and neuropathologic comorbidities were calculated using Fisher's exact test. False Discovery Rate (FDR) correction was used for multiple comparison testing, and statistical significance was set at $\alpha = 0.05$.

RESULTS

Demographic features of NT, PART, and ADNC groups

The ADNC cohort was older on average than the NT cohort (80.2±0.2 versus 78.6±0.5; $p = 0.0496$), while the average age of the PART cohort(82.0±0.8) was greater than both the NT cohort ($p = 0.0006$) and the ADNC cohort ($p = 0.0203$) (Table 1). No significant differences were observed in terms of gender, race, or years of education. There was a higher prevalence of *APOE* $\varepsilon 2$ alleles in the PART cohort as compared to ADNC subjects ($p < 0.0001$) and NT subjects ($p = 0.0425$) and a lower prevalence of APOE $\varepsilon 4$ alleles compared to ADNC subjects ($p < 0.0001$). The ADNC cohort had a significantly lower proportion of cases with at least one APOE $\varepsilon 2$ allele ($p < 0.0001$) and a significantly higher proportion of cases with at least one APOE $\varepsilon 4$ allele ($p < 0.0001$) compared to the group without tauopathy. In addition, (1.6%), while the ADNC cohort had 305 cases with APOE $\varepsilon 4/\varepsilon 4$ (11.9%; $p < 0.0001$) and only 6 cases with APOE $\varepsilon 2/\varepsilon 2$ (0.2%; $p = 0.0184$).

Frequency and effects of comorbidities on cognition in NT, PART, and ADNC groups

The ADNC cohort had significantly higher frequencies of stage 2–3 (limbic or neocortical) LBD as compared to the NT (32.0% versus 6.9%; $p < 0.0001$) and PART (13.9%; $p < 0.0001$) cohorts, and the PART group had significantly higher LBD compared to the NT group ($p = 0.0308$). Similar findings were present with respect to cerebrovascular disease, where ADNC had the highest prevalence (56.3%) compared to PART (41.7%) and NT (25.0%), as well as with respect to arteriolosclerosis, where ADNC had a prevalence of 44.0% compared to PART (35.6%) and NT (24.6%) (Table 2 and Fig. 1). No significant difference was found in the prevalence of LATE-NC between any of these groups.

Previous studies have shown that comorbid neuropathologic findings have significant influence on the overall cognitive state of the patient [7, 8, 11, 12, 14, 15, 17, 19], although it is generally unknown to what extent each specific neuropathologic entity contributes to cognition in a given patient. In the subjects without tauopathy, LATE-NC and cerebrovascular disease both have a significantly deleterious effect on cognition in terms of global CDR, CDR sum of boxes, and MMSE (Table 3). Cases with PART alone do not differ from the NPI group of cases in terms of CDR, CDR sum of boxes, or MMSE, however LATE-NC, LBD, and CVD all cause significant cognitive impairment when combined with PART pathology. As expected, patients with ADNC have significantly worse cognition than both the no pathology identified (NPI) group and PART group in terms of global CDR, CDR sum of boxes, and MMSE, and the presence of LATE-NC, LBD, and CVD generally causes additional cognitive impairment in these patients (Table 3).

Differing neuropsychological profiles in NPI, PART, and ADNC groups

In terms of more detailed neuropsychological analysis of PART in comparison to NPI and ADNC subjects, we evaluated representative variables comprising attention, processing speed, executive function, memory, and language [62]. When excluding cases with LATE-NC, LBD, and CVD from the NPI, PART, and ADNC cohorts, the ADNC group had similarly worse outcomes across all clinical measures except TMT-A and TMT-B, which were statistically equivalent to the PART cohort. The PART cohort was not statistically different from the NPI cohort in terms of global CDR ($p = 0.5381$), CDR sum of boxes ($p = 0.5838$), or MMSE ($p = 0.2737$); however, PART subjects performed significantly worse than NPI patients in terms of processing speed (TMT-A $p = 0.0085$; WAIS DS $p = 0.0021$) and executive function (TMT-B $p = 0.0488$) (Table 4). When converting the neuropsychological variables to z-scores (Supplementary Table 1), the PART cohort performed significantly worse than the NPI cohort in terms of attention (digit span forward and digit span backward) and processing speed (TMT-A and WAIS DS). No other memory, attention, or language-related variables were significantly different between the PART and NT groups.

PART cases with Braak stage III-IV were not significantly different from the NPI cohort in terms of global CDR ($p = 0.4258$), CDR sum of boxes ($p = 0.3806$), or MMSE ($p = 0.3805$), but did perform significantly worse than NPI cases in terms of processing speed (TMT-A $p < 0.0001$; WAIS DS $p = 0.0018$), executive function (TMT-B p=0.0013), and language (animal fluency $p = 0.0016$; vegetable naming $p = 0.0066$; BNT $p = 0.0016$) (Supplementary Table 2). In contrast, few significant differences were observed between PART cases with Braak I-II, ADNC cases with Braak I-II, and cases without pathology, although measures of attention appear to be selectively worse in ADNC compared to PART ($p = 0.0009$) and TMT-A is worse in ADNC compared to NPI ($p = 0.0073$) (Supplementary Table 3).

Importantly, neuropathologic comorbidities have variable effects on cognitive and neuropsychological performance in PART subjects (Table 5 and Supplementary Table 4). Both LATE-NC and LBD have significantly deleterious effect on global CDR, and there is a non-significant trend toward worse global CDR in PART patients with documented cerebrovascular disease. CDR sum of boxes (and the individual component domains) and MMSE are further impaired by LATE-NC, LBD, and CVD. Additionally these three comorbid disease processes have variable deleterious effects in terms of memory, attention, processing speed, and language function. Notably, the patients with PART and LBD performed particularly poorly in terms of processing speed (TMT-A and WAIS DS) and executive function (TMT-B), however this may be due in part to visuospatial issues associated with LBD or to more selective impairment in motor skills secondary to LBD in these patients, especially since subjects with definite PART and brainstem-only LBD (n = 13) also had significantly worse WAIS DS (30.2±1.1; $p = 0.0218$) and TMT-B (169.8±20.4; $p = 0.0169$), although they had statistically equivalent TMT-A (59.3±5.1; $p = 0.1562$), without other significant differences in cognitive domains.

DISCUSSION

In recent years, there has been mounting evidence suggesting that primary age-related tauopathy, previously termed “tangle-only senile dementia” and “tangle-predominant senile dementia,” represents an entity distinct from AD, rather than simply a precursor to it, with studies demonstrating significant differences in the radiologic, neuropathologic, and genetic profiles between PART and ADNC [20, 22, 26, 34, 67, 68]. While clinical symptoms and cognitive impairment in AD is thought to be most closely related to the topographic distribution of p-tau throughout the brain quantified by Braak staging, this does not appear to be the case with PART. Instead, the cognitive status in PART patients is determined primarily by overall p-tau-burden in the hippocampus, as well as the presence of comorbid neuropathologies, including white matter pathology, ARTAG, LATE-NC, and CVD [22, 27, 40, 41]. Recent studies have shown that while PART does appear to have a deleterious effect on cognition, PART patients have a significantly slower rate of cognitive decline after becoming symptomatic comparted to patients with ADNC, and have relative sparing of a number cognitive domains, including semantic memory, language, and attention [31, 35, 36, 38]. In this study, we used the NACC dataset to evaluate the cognitive profile of a cohort with definite PART, as compared to patients with no identified tauopathy (or other neurodegenerative pathologies) and patients with ADNC, and investigated the cognitive contributions of some of the more common neuropathologic comorbidities seen in PART.

When excluding LATE-NC, LBD, and CVD as comorbid pathologies, there were few significant differences in the cognitive profile between definite PART cases compared to NPI cases, including statistically equivalent global CDR, CDR sum of boxes, and MMSE tests (Table 4). The PART patients did perform significantly worse in measures of processing speed and executive function compared to the NPI cohort, and PART patients with Braak stage III-IV also had significantly worse performance in measures of language (Supplementary Table 2), while few meaningful differences were noted in patients with Braak stage I-II (Supplementary Table 3). Importantly, however, the majority of the cognitive features were significantly worse in ADNC than in PART (Table 4), allowing for a level of clinical discrimination between the two neuropathologic entities. It is interesting that the PART cohort performed worse than the NPI cohort in terms of WAIS CD, TMT-A, and TMT-B tests, which were previously shown to be progressively affected by Braak stage in PART patients [63]. These tests assess processing speed and executive function, but are also dependent on relatively intact visuospatial function, which may be affected in both PART and LBD, both of which show an early predilection for the CA2 hippocampal subregion [22, 63, 69, 70]. The precise function of the CA2 subfield is unclear, but studies have shown that it has functions in social memory [71–73], face-name pair encoding and retrieval [74], and visuospatial memory [39, 75, 76], suggesting that the particular cognitive and neuropsychological deficits found in this PART cohort may be due, at least in part, to the characteristic CA2 neurofibrillary degeneration pattern seen in these patients [22, 24, 25]. In addition, ADNC cases with low Braak stage (“early” AD) do not have selective deficits in the same cognitive domains as PART (Supplementary Tables 2, 3), suggesting that the particular differences in patterns of hippocampal pathology may result in different clinical phenotypes, particularly early in the disease course.

As demonstrated in numerous other studies [7, 8, 10, 11, 13–16, 18, 19], many autopsy-confirmed cases of ADNC have additional neurodegenerative findings that may affect cognition to various degrees. Our results demonstrate that LBD and various forms of CVD are more common in ADNC compared to PART and subjects without tauopathy, and more common in PART than patients without tauopathy, while the frequency of LATE-NC does not differ significantly between these groups (Table 2). These other neuropathologic findings further impair cognition in PART, ADNC, and NT cohorts in terms of CDR and MMSE (Table 3), and have variably deleterious effects on logical memory, attention, processing speed, language, and executive function (Table 5). Interestingly, while the presence of LATE-NC and CVD both cause cognitive impairment in subjects with PART, the presence of PART does not appear to cause additional cognitive impairment in subjects with LATE-NC and CVD, suggesting that these comorbidities may drive the more significant cognitive decline in PART patients.

As previous studies have also noted, the APOE profile differs between PART and ADNC [30, 31, 36]. In the current population, there are significantly more cases with at least one APOE ε2 allele and with two APOE ε2 alleles in the PART population and significantly fewer cases with one APOE ε2 and with two APOE ε2 alleles compared to the ADNC population. Given the role of APOE in the regulation of Aβ metabolism in the brain, the relatively reduced risk for Aβ accumulation with APOE ε2, and the increased risk for Aβ accumulation with APOE ε4 [77–79], this differing genetic profile between PART and ADNC is not surprising. However, these findings do suggest that PART and ADNC may represent distinct disease processes, where the p-tau deposition in PART is driven by mechanisms unrelated to Aβ deposition, unlike in ADNC [21, 24]. In addition, the PART patients in this cohort have a significantly higher mean age compared to ADNC patients (and have been shown to represent the “oldest old” in other cohorts), suggesting that this tauopathy does not simply represent “pre-ADNC” which will eventually develop Aβ plaques and convert to ADNC [21, 45].

A significant limitation to this study is that the NACC dataset is not representative of the general population. Due to collection methods at nation-wide Alzheimer’s Disease Research Centers, the cohorts are enriched for patients with more severe neuropathologic findings, more frequent and severe dementia, more APOE ε4 alleles, and more rare diseases compared to the general population. The population is also enriched for Caucasian patients with higher educational status than the general population and lacks a representative number control patients. Given the length of time NACC cases have been collected historically and the series of revisions to the NP and UDS variables, as well as the identification of new pathologic proteins, development of new antibodies, development of new classification systems, and recognition of new entities within this time period there are relevant pathologic variables which are unassessed for a subset of cases, particularly with LATE-NC, a diagnosis only formally codified in 2019 [51]. In addition, the pathologic variables assessed, particularly those related to AD pathology, assess primarily the overall distribution of pathology throughout the brain to a greater extent than the density or severity of pathology within a given region, which has been shown to be a particularly important predictor of cognitive status in PART [40, 42].

Our findings suggest clinical features which may represent the pure contribution of PART neuropathologic changes, and provide cognitive and neuropsychological differences between PART and AD. While PART cohorts have significantly better overall cognition than ADNC cohorts, processing speed and executive function appear to be selectively impaired in PART patients. Given the differing patterns of p-tau deposition in the hippocampus of subjects with PART and ADNC, as well as the more limited p-tau distribution and lack of Aβ, these clinical findings may help to provide functional insight into hippocampal subregions and other brain regions, as well as provide insight into mechanisms by which diffuse and neuritic Aβ plaques may contribute to cognitive impairment. Overall, these data help to further establish PART as an entity distinct from ADNC in terms of demographic, genetic, neuropathologic, and clinical features.

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DATA AVAILABILITY

The data presented in this manuscript is derived from the National Alzheimer's Coordinating Center (NACC) dataset, and is available upon request from https://naccdata.org/.

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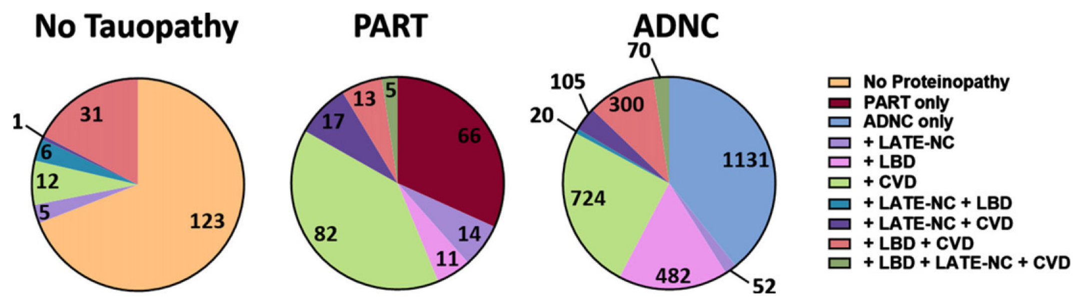

Fig. 1.

Pie charts demonstrating the relative number of comorbid pathologies in cases with no tauopathy, PART, and ADNC.

Table 1

Demographic data in individuals with ADNC, PART, and no identified tauopathy

	No tauopathy (NT)	PART	ADNC	*P* (NT versus PART)	*P* (NT versus ADNC)	*P* (PART versus ADNC)
n	178	208	2884	–	–	–
Mean age (y)	78.6 ± 0.5	82.0 ± 0.8	80.2 ± 0.2	**=0.0006**	**=0.0496**	**=0.0203**
Gender (M:F)	110:68	124:84	1572:1312	=0.6772	=0.0625	=0.1704
Race				=0.8391	=0.7393	=0.2707
Caucasian	93.7%	92.8%	94.3%			
African American/Black	4.1%	5.3%	4.5%			
Asian	1.6%	1.4%	0.8%			
Hawaiian/Pacific Islander	0.4%	0.4%	0.1%			
Education (y)	16.8 ± 0.8	16.7 ± 0.6	16.1 ± 0.2	=0.9191	=0.3986	=0.4311
APOE Status						
≥1 *APOE* ε2 allele	15.7%	24.5%	4.2%	**=0.0425**	**<0.0001**	**<0.0001**
≥1 *APOE* ε4 allele	12.4%	8.2%	51.3%	=0.1803	**<0.0001**	**<0.0001**

Table 2

Comorbidities in individuals with ADNC, PART, and no tauopathy

	No tauopathy (NT)	PART	ADNC	*P* (NT versus PART)	*P* (NT versus ADNC)	*P* (PART versus ADNC)
LATE-NC, Stage 2–3*	39.5%	26.9%	27.0%	=0.1283	=0.0806	=0.9981
LBD, Stage 2–3	6.9%	13.9%	32.0%	**=0.0308**	**<0.0001**	**<0.0001**
Cerebrovascular Disease	25.0%	41.7%	56.3%	**=0.0004**	**<0.0001**	**=0.0001**
Infarct	9.1%	17.3%	17.5%	**=0.0243**	**=0.0035**	=0.9727
Hemorrhage*	5.6%	2.1%	7.8%	=0.1197	=0.5909	**=0.0051**
White Matter Rarefaction*	30.6%	22.0%	27.0%	=0.2580	=0.6236	=0.2241
Arteriolosclerosis, mod-severe*	24.6%	35.6%	44.0%	**=0.0288**	**<0.0001**	**=0.0270**

* note: these variables not assessed in all subjects.

Table 3

Comparison of cognition in cohorts with various combinations of neuropathologic findings

	Global CDR	CDR Sum of Boxes	MMSE
No Pathology Identified	0.9 ± 0.1	4.8 ± 0.3	26.3 ± 0.3
LATE-NC	2.0 ± 0.2	11.6 ± 0.9	19.0 ± 1.6
p (versus NPI)	**<0.0001**	**<0.0001**	**<0.0001**
LBD	–	–	–
p (versus NPI)	–	–	–
CVD	1.3 ± 0.1	6.9 ± 0.4	22.2 ± 0.7
p (versus NPI)	**<0.0001**	**<0.0001**	**<0.0001**
PART	0.8 ± 0.1	4.4 ± 0.6	25.6 ± 0.5
p (versus NPI)	=0.5381	=0.5838	=0.2737
PART + LATE-NC	1.8 ± 0.2	10.2 ± 1.1	21.4 ± 1.2
p (versus PART)	**<0.0001**	**<0.0001**	**=0.0004**
PART + LBD	1.7 ± 0.2	9.5 ± 1.2	21.6 ± 1.1
p (versus PART)	**<0.0001**	**<0.0001**	**=0.0002**
PART + CVD	1.3 ± 0.1	7.0 ± 0.6	22.3 ± 0.6
p (versus PART)	=0.0727	=0.0051	=0.0003
ADNC	2.0 ± 0.02	11.6 ± 0.1	15.4 ± 0.2
p (versus NPI)	**<0.0001**	**<0.0001**	**<0.0001**
ADNC + LATE-NC	2.3 ± 0.1	13.6 ± 0.3	14.5 ± 0.5
p (versus ADNC)	**<0.0001**	**<0.0001**	=0.0651
ADNC + LBD	2.3 ± 0.03	13.2 ± 0.2	13.3 ± 0.3
p (versus ADNC)	**<0.0001**	**<0.0001**	**<0.0001**
ADNC + CVD	2.1 ± 0.03	12.1 ± 0.2	14.8 ± 0.3
p (versus ADNC)	**=0.0062**	**=0.0282**	=0.1002

Table 4

Comparison of cognition in individuals with pure ADNC, pure PART, and no identified pathologies

	No Pathology Identified (NPI)	Pure PART	Pure ADNC	Adj. *p* (NPI versus PART)	Adj. *p* (NPI versus ADNC)	Adj. *p* (PART versus ADNC)
Global CDR	0.9 ± 0.1	0.8 ± 0.1	2.0 ± 0.02	=0.5381	**<0.0001**	**<0.0001**
CDR Sum of Boxes	4.8 ± 0.3	4.4 ± 0.6	11.6 ± 0.1	=0.5838	**<0.0001**	**<0.0001**
Memory	1.0 ± 0.1	0.8 ± 0.1	2.0 ± 0.02	=0.2579	**<0.0001**	**<0.0001**
Orientation	0.8 ± 0.1	0.6 ± 0.1	1.9 ± 0.02	=0.2579	**<0.0001**	**<0.0001**
Judgement	0.8 ± 0.2	0.8 ± 0.1	2.0 ± 0.02	=0.9221	**<0.0001**	**<0.0001**
Community Affairs	1.0 ± 0.1	0.7 ± 0.1	1.9 ± 0.02	=0.0522	**<0.0001**	**<0.0001**
Home & Hobbies	1.1 ± 0.2	0.8 ± 0.1	2.0 ± 0.02	=0.2579	**<0.0001**	**<0.0001**
Personal Care	0.9 ± 0.1	0.7 ± 0.1	1.8 ± 0.02	=0.2579	**<0.0001**	**<0.0001**
MMSE	26.3 ± 0.3	25.6 ± 0.5	15.4 ± 0.2	=0.2737	**<0.0001**	**<0.0001**
Memory						
Logical Memory Immediate Recall	13.6 ± 1.0	13.0 ± 0.6	7.4 ± 0.1	=0.6128	**<0.0001**	**<0.0001**
Logical Memory Delayed Recall	11.9 ± 1.0	11.5 ± 0.6	5.5 ± 0.1	=0.7051	**<0.0001**	**<0.0001**
Attention						
Digit Span Forward	10.9 ± 1.0	9.1 ± 0.5	7.4 ± 0.1	=0.2289	**<0.0001**	**<0.0001**
Digit Span Backward	8.7 ± 1.1	6.3 ± 0.6	4.3 ± 0.1	=0.1324	**<0.0001**	**<0.0001**
Processing Speed						
TMT-A	42.2 ± 1.3	51.2 ± 2.3	58.1 ± 0.7	**=0.0085**	**<0.0001**	=0.0690
WAIS DS	40.4 ± 1.0	35.1 ± 0.9	31.2 ± 0.3	**=0.0021**	**<0.0001**	**=0.0148**
Executive						
TMT-B	118.5 ± 3.4	132.1 ± 5.6	149.1 ± 1.6	**=0.0488**	**<0.0001**	=0.0513
Language						
Animals	15.7 ± 0.3	14.8 ± 0.6	11.8 ± 0.1	=0.2579	**<0.0001**	**<0.0001**
Vegetables	12.9 ± 0.3	12.3 ± 0.4	9.8 ± 0.1	=0.2737	**<0.0001**	**<0.0001**
BNT	26.5 ± 0.3	27.1 ± 0.4	22.8 ± 0.1	=0.2737	**<0.0001**	**<0.0001**

Table 5

Comparison of cognition in individuals with PART and variable comorbidities

	Pure PART	PART + LATE-NC	Adj. *p*	PART + LBD	Adj. *p*	PART + CVD	Adj. *p*
Global CDR	0.8 ± 0.1	1.8 ± 0.2	**<0.0001**	1.7 ± 0.2	**<0.0001**	1.3 ± 0.1	=0.0727
CDR Sum of Boxes	4.4 ± 0.6	10.2 ± 1.1	**<0.0001**	9.5 ± 1.2	**<0.0001**	7.0 ± 0.6	**=0.0051**
Memory	0.8 ± 0.1	1.6 ± 0.2	**=0.0006**	1.3 ± 0.2	=0.0535	1.1 ± 0.1	**=0.0378**
Orientation	0.6 ± 0.1	1.6 ± 0.2	**<0.0001**	1.4 ± 0.2	**=0.0016**	1.1 ± 0.1	**=0.0006**
Judgement	0.8 ± 0.1	1.8 ± 0.2	**<0.0001**	1.6 ± 0.2	**=0.0016**	1.2 ± 0.1	**=0.0059**
Community Affairs	0.7 ± 0.1	1.8 ± 0.2	**<0.0001**	1.6 ± 0.3	**=0.0012**	1.2 ± 0.1	**=0.0006**
Home & Hobbies	0.8 ± 0.1	1.8 ± 0.2	**<0.0001**	1.7 ± 0.3	**=0.0012**	1.3 ± 0.1	**=0.0006**
Personal Care	0.7 ± 0.1	1.7 ± 0.2	**<0.0001**	1.6 ± 0.3	**=0.0012**	1.1 ± 0.1	**=0.0059**
MMSE	25.6 ± 0.5	21.4 ± 1.2	**=0.0004**	21.6 ± 1.1	**=0.0002**	22.3 ± 0.6	**=0.0003**
Memory							
Logical Memory Immediate Recall	13.0 ± 0.6	8.2 ± 0.8	**<0.0001**	9.2 ± 0.9	**=0.0008**	10.3 ± 0.6	**=0.0020**
Logical Memory Delayed Recall	11.5 ± 0.6	7.9 ± 0.9	**=0.0006**	7.8 ± 1.1	**=0.0014**	9.2 ± 0.6	**=0.0082**
Attention							
Digit Span Forward	9.1 ± 0.5	8.4 ± 0.4	=0.1187	8.2 ± 0.4	=0.1098	8.0 ± 0.3	=0.0511
Digit Span Backward	6.3 ± 0.6	5.4 ± 0.5	=0.1150	5.5 ± 0.3	=0.1537	5.8 ± 0.3	=0.4312
Processing Speed							
TMT-A	51.2 ± 2.3	64.4 ± 6.2	**=0.0063**	68.5 ± 10.3	**=0.0129**	59.9 ± 3.6	=0.0559
WAIS DS	35.1 ± 0.9	33.3 ± 0.4	=0.0656	23.1 ± 1.4	**<0.0001**	30.1 ± 1.3	**=0.0030**
Executive							
TMT-B	132.1 ± 5.6	150.5 ± 7.3	=0.0579	158.2 ± 14.4	**=0.0202**	140.7 ± 3.9	=0.1975
Language							
Animals	14.8 ± 0.6	11.7 ± 1.3	**=0.0063**	11.9 ± 1.0	**=0.0061**	13.3 ± 0.8	**=0.1521**
Vegetables	12.3 ± 0.4	9.1 ± 0.8	**=0.0001**	9.2 ± 0.7	**<0.0001**	10.5 ± 0.5	**=0.0074**
BNT	27.1 ± 0.4	24.2 ± 1.1	**=0.0014**	26.6 ± 0.7	=0.1907	24.8 ± 0.7	**=0.0083**