

Differences in Cognitive Impairment in Primary Age-Related Tauopathy Versus Alzheimer Disease

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Abstract

This study examined differences in neuropsychological test scores between individuals with primary age-related tauopathy (PART) and Alzheimer disease (AD) using cross-sectional data from the National Alzheimer's Coordinating Center. Linear regression tested for differences in 4 cognitive domains stratified by cognitive status (global Clinical Dementia Rating [CDR]). The sample included 240 participants with no neuritic plaques (NP) (definite PART), 186 with

sparse NP (possible PART), and 510 with moderate/frequent NP (AD). Four cognitive domain *z*-score outcome variables (memory, attention, executive function, and semantic memory/language) were calculated using 12 neuropsychological tests. Definite PART participants had a sparing of semantic memory/language compared to those with AD, with a mean adjusted *z*-score difference of 0.37 (95% confidence interval [CI]: 0.16–0.58) for those with CDR = 0.5 or 1 and of 0.92 (CI: 0.22–1.63) for those with CDR = 2 or 3. Compared to participants with AD, definite PART participants with CDR = 0.5 or 1 had sparing of memory (adjusted *z*-score difference: 0.61; CI: 0.39–0.84) and definite PART participants with CDR = 2 or 3 had sparing of attention (adjusted *z*-score difference: 0.76; CI: 0.09–1.43). Patterns of cognitive impairment differed between definite PART and AD, suggesting significant differences in clinical presentation between individuals from these 2 groups.

Key Words: AD, Alzheimer disease, Cognition, Cognitive, Neuropathology, PART, Primary age-related tauopathy.

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INTRODUCTION

A variety of neuropathologic changes underlie the cognitive patterns observed in mild cognitive impairment and dementia (1–4). Primary age-related tauopathy (PART), one such pattern of neuropathologic change associated with cognitive impairment, is characterized by the presence of neurofibrillary tangles (NFT) composed of tau protein in regions comparable to early- to moderate-stage Alzheimer disease (AD), independent of amyloid plaque deposition (5, 6). Higher NFT burden in individuals with PART has been associated with more rapid decline in episodic and semantic memory/language and processing speed/attention (7) and worse scores on the WAIS-R Block Design and Trail Making Tests (8). Otherwise, cognitive changes associated with PART have been minimally addressed. Furthermore, few studies have investigated differences in cognitive domain scores between those with PART and AD. One study suggested that Mini-Mental State Exam (MMSE) scores are relatively preserved at higher Braak stages in PART compared to AD (defined as moderate to frequent neuritic plaques [NP]), but the study did not control for potential confounding factors such as apolipoprotein E (*APOE*) genotype and did not examine differences in sensitive neuropsychological tests (6).

Hence, we sought to compare neuropsychological test scores for several cognitive domains (i.e. episodic memory, attention, executive function, semantic memory/language) among individuals who subsequently had either PART or AD at autopsy, and to examine their score differences by disease stage. By so doing, we aimed to increase understanding of the cognitive consequences of the biologic changes occurring in PART and to test the hypothesis that differences in cognition between PART and AD can be demonstrated during life.

MATERIALS AND METHODS

Sample

The study sample originated from the National Alzheimer's Coordinating Center's (NACC) Uniform Data Set (UDS) (9) and Neuropathology Data Set (10, 11). UDS clinical data, including demographics, health history, clinical symptoms, neuropsychological test scores, and diagnoses have been collected longitudinally on participants at approximately 30 Alzheimer Disease Centers (ADCs) since September 2005. A subset of UDS participants consent to autopsy and have neuropathological exam data collected on standardized forms. Data collected up through the end of August 2017 were included in this study.

Standard Protocol Approvals, Registration, and Patient Consents

Each ADC obtained written informed consent from all participants and use of NACC data for research has been approved by University of Washington's Institutional Review Board.

Participants

Our sample was restricted to participants with: (i) a neuropathological exam; (ii) nonmissing data on NP; (iii) a UDS visit conducted ≤ 2 years of autopsy; (iv) Version 2 of the neuropsychological battery at the last visit before death; (v) ≥ 1 nonmissing calculated cognitive domain z -score from the last visit before death; and (vi) none of the following comorbidities: clinical and neuropathological Lewy body disease (including Parkinson disease), Huntington disease, clinical or neuropathological prion disease, clinical corticobasal syndrome or progressive supranuclear palsy, frontotemporal lobar degeneration (FTLD) with tau inclusions, FTLD with transactive response DNA-binding protein 43 (TDP-43), or FTLD not otherwise specified. Participants were stratified by cognitive status at their last visit before death (Clinical Dementia Rating [CDR] = 0, CDR = 0.5 or 1, or CDR = 2 or 3) and by neuropathologic lesion burden at autopsy as follows: definite PART (i.e. no NP), possible PART (i.e. sparse NP), and AD (moderate to frequent NP). These groups were based on a Consortium to Establish a Registry for Alzheimer's Disease (CERAD) score for neocortical NP density (plaques with argyrophilic, thioflavin S-positive or tau-positive dystrophic neurites with/without dense amyloid cores [12]), which ADCs ascertain using standardized definitions/techniques (13, 14). Unlike Thal phase for amyloid deposits, which is available for a smaller

subset of autopsied participants, CERAD NP are available for the vast majority and have been suggested as reasonable alternatives in classifying PART (6).

We describe the sample according to demographic, clinical, and neuropathologic characteristics, including Braak stage for neurofibrillary degeneration (15), age at last visit (years), sex, education (years), nonwhite race (yes/no), ≥ 1 *APOE* $\epsilon 4$ allele, family history of cognitive impairment, global CDR at last visit, self-reported history of stroke, hypertension, depression, diabetes, and traumatic brain injury, and vascular brain injury (VBI) at autopsy (hemorrhage, microbleed, infarct/lacune, or microinfarct). Braak stage, expected to be associated with cognitive impairment (5), was described for the sample and controlled for in multivariable analyses. The definite PART, possible PART, and AD groups were compared on these characteristics using unadjusted logistic regression, with $\alpha = 0.05$ determining statistical significance.

Neuropsychological Tests

The UDS neuropsychological test battery (Version 2) (16) was used to calculate z -scores for 4 cognitive domains and a z -score for global cognition. Unadjusted z -scores were calculated for each of 12 neuropsychological tests by comparing to the mean test scores of 10 988 individuals with a global CDR = 0 at their initial visit (i.e. norms sample). To obtain a z -score for each test, we subtracted the norms sample's mean score from each individual's raw neuropsychological test score and divided by the standard deviation of the norms sample's score. Then for each individual, the cognitive domain scores were determined by calculating a simple average of Logical Memory Immediate and Delayed z -scores for the episodic memory domain; Digit Span Forward and Backward correct trials and span length z -scores for the attention domain; Trail Making Test Parts A and B and Digit Symbol z -scores for the executive function domain; and Animals, Vegetables, and Boston Naming test z -scores for the semantic memory/language domain. These 4 composites were previously determined for the UDS neuropsychological battery using a factor analysis (17). We diverge from that prior factor analysis by referring to "semantic memory/language" instead of language because word fluency tasks and naming tasks additionally reflect semantic memory/retrieval and are distinct from specific language impairments in aging populations (18, 19). A simple average of the z -scores for the 4 cognitive domains provided the z -score for the global composite. The mean unadjusted cognitive domain scores were stratified by cognitive status at the last visit before death and comparison group (Supplementary Data Table S1).

Statistical Analyses

Unadjusted and adjusted linear regression analyses with generalized estimating equations (accounting for clustering by Center), employing an exchangeable working correlation structure, were run to compare cognitive domain z -scores between those with definite or possible PART and AD (using 2 dummy variables with AD as reference group). As differences

TABLE 1. Sample Demographics in Primary Age-Related Tauopathy Versus Alzheimer Disease

Characteristic*	Definite PART	Possible PART	AD	Definite PART Versus AD p Value [†]	Possible PART Versus AD p Value [†]
Sample size, n	240	186	510	NA	NA
Age at last visit (years), n (%)					
<60	9 (3.8%)	0 (0.0%)	16 (3.1%)	0.29	<0.001
60–69	15 (6.3%)	9 (4.8%)	30 (5.9%)		
70–79	44 (18.3%)	27 (14.5%)	94 (18.4%)		
80–89	86 (35.8%)	67 (36.0%)	240 (47.1%)		
90+	86 (35.8%)	83 (44.6%)	130 (25.5%)		
Male sex, n (%)	115 (47.9%)	87 (46.8%)	281 (55.1%)	0.07	0.05
Education (years), mean (SD)	15.3 (2.7)	14.8 (3.4)	15.3 (3.2)	0.95	0.13
Nonwhite race (yes versus no), n (%)	15 (6.3%)	13 (7.0%)	33 (6.5%)	0.92	0.82

Abbreviations: PART, primary age-related tauopathy; AD, Alzheimer disease; NA, not applicable.

*Missing data (definite PART, possible PART, AD): education (n = 4; n = 0; n = 3); race (n = 2; n = 0; n = 3).

[†]Unadjusted logistic regression.

Bold = statistically significant at p < 0.05.

between definite PART and AD groups might vary significantly based on cognitive status, analyses were stratified by global CDR score. The multivariable models controlled for variables that are either common confounders in dementia research or were differentially distributed between the groups in our study (Tables 1 and 2): age at last visit; sex; education; ≥ 1 APOE $\epsilon 4$ allele; family history of cognitive impairment; history of hypertension, stroke, diabetes, or traumatic brain injury; and Braak stage (dichotomized as 0–II and III–VI due to small numbers with definite PART and high Braak stage and with AD and low Braak stage). In addition, we present the same adjusted analyses for those with CDR = 0 or CDR = 0.5–1 stratified by Braak stages (I–II, III–IV) instead of controlling for Braak stage (sample too sparse to examine CDR = 2–3 or Braak stages V–VI). Statistical significance was based on alpha = 0.05.

In post hoc analyses, we reran the multivariable linear regression analyses with each semantic memory test z-score (Animals, Vegetables, Boston Naming test) entered as separate outcome variables to investigate in more detail the finding that semantic memory/language was the most notably different domain between PART and AD. Each regression model included individuals who were not missing the examined cognitive domain z-score. Additional sensitivity analyses included rerunning the adjusted models after: (1) redefining definite PART based on the absence of diffuse plaques instead of NP, and (2) removing vascular risk factors (hypertension, diabetes, stroke) as covariates and adding a variable for VBI observed at autopsy. The former sensitivity analysis was conducted to determine if the results would change significantly after defining PART in a manner consistent with Thal phase 0. Data on Thal phase were only collected in the most recent version of the NP Form and thus were missing for 80% of the sample. Therefore, data on diffuse plaques, which were collected since the inception of the NP Form, were used in the place of Thal phase.

RESULTS

The sample included 240 participants with definite PART, 186 with possible PART, and 510 with AD (Fig. 1; Table 1). A larger percentage with possible PART were ≥ 90

years old (last visit before death), compared to AD (Table 1; Fig. 2). No significant differences were observed by sex (male: 48% definite PART; 47% possible PART; 55% AD). The majority with definite PART had Braak stages I–II, the majority with possible PART had Braak stages III–IV, and the majority with AD had Braak stages V–VI (Table 2). Compared to AD, those with definite or possible PART less often had ≥ 1 APOE $\epsilon 4$ allele. A family history of cognitive impairment was reported less often in definite PART versus AD. Higher global CDR scores indicating greater impairment were more likely in AD than in definite and possible PART. Compared to AD, those with definite PART were more likely to report a history of stroke, hypertension, and diabetes. Likewise, compared to AD, those with possible PART were more likely to report a history of stroke, hypertension, and traumatic brain injury, and were more likely to have VBI at autopsy. The unadjusted cognitive domain z-scores by group and cognitive status are reported in Supplementary Data Figure S1 and Table S1.

In the unadjusted linear regression analyses, individuals with definite PART scored significantly better than those with AD on episodic memory regardless of cognitive status (Supplementary Data Table S2). In those with CDR = 0.5–1 and CDR = 2–3, individuals with definite PART scored significantly better than those with AD on the global composite and semantic memory/language domain. In addition, in those with CDR = 2–3, individuals with definite PART scored better than those with AD on attention and executive function. Compared to AD, individuals with possible PART scored worse on attention among those with CDR = 0, better on episodic memory among those with CDR = 0.5–1, and better on semantic memory/language in those with CDR = 2–3.

In the adjusted linear regression analyses comparing individuals with definite PART and AD, there were no significant differences in cognitive domain scores among those with CDR = 0 (Table 3; Fig. 3). However, compared to AD, the definite PART group scored better on the global composite, episodic memory, and semantic memory/language domains among those with CDR = 0.5–1, and the definite PART group

TABLE 2. Braak Stage and Clinical Characteristics in Primary Age-Related Tauopathy Versus Alzheimer Disease

Characteristic*	Definite PART n (%)	Possible PART n (%)	AD n (%)	Definite PART Versus AD p Value [†]	Possible PART Versus AD p Value [†]
Braak stage					
0	35 (14.8%)	5 (2.7%)	3 (0.6%)	<0.001	<0.001
I–II	126 (53.4%)	53 (28.5%)	63 (12.4%)		
III–IV	71 (30.1%)	94 (50.5%)	158 (31.0%)		
V–VI	4 (1.7%)	34 (18.3%)	285 (56.0%)		
Presence of ≥ 1 APOE $\epsilon 4$ allele	31 (13.6%)	60 (34.3%)	212 (45.3%)	<0.001	0.01
Family history, cognitive impairment	93 (42.5%)	93 (52.3%)	273 (56.8%)	0.001	0.30
Global CDR score, last visit					
0	122 (50.8%)	64 (34.4%)	74 (14.5%)	Ref.	Ref.
0.5	60 (25.0%)	61 (32.8%)	116 (22.8%)	<0.001	0.03
1	38 (15.8%)	29 (15.6%)	127 (24.9%)	<0.001	<0.001
2	14 (5.8%)	24 (12.9%)	123 (24.1%)	<0.001	<0.001
3	6 (2.5%)	8 (4.3%)	70 (13.7%)	<0.001	<0.001
History of stroke	45 (18.8%)	37 (20.0%)	66 (13.1%)	0.04	0.03
History of hypertension	173 (72.4%)	140 (76.1%)	329 (64.6%)	0.04	0.005
History of depression	92 (38.7%)	60 (32.4%)	192 (37.9%)	0.84	0.19
History of diabetes	49 (20.4%)	28 (15.1%)	61 (12.0%)	0.003	0.27
History of traumatic brain injury	30 (12.5%)	34 (18.7%)	58 (11.5%)	0.70	0.02
Vascular brain injury at autopsy [‡]	106 (44.2%)	95 (51.1%)	205 (40.2%)	0.30	0.01

Abbreviations: APOE, apolipoprotein E; CDR, Clinical Dementia Rating; PART, primary age-related tauopathy; AD, Alzheimer disease; NA, not applicable.

*Missing data (definite PART, possible PART, AD): APOE genotype (n = 12; n = 11; n = 42); family history (n = 21; n = 8; n = 29); stroke (n = 1; n = 1; n = 6); hypertension (n = 1; n = 2; n = 1); depression (n = 2; n = 1; n = 3); diabetes (n = 0; n = 1; n = 1); TBI (n = 0; n = 4; n = 7); Braak stage (n = 4; n = 0; n = 1).

[†]Unadjusted logistic regression.

[‡]Vascular brain injury included hemorrhage, microbleed, infarct/lacune, and microinfarct.

Bold = statistically significant at p < 0.05.

scored better on attention and semantic memory/language among those with CDR = 2–3. Individuals with possible PART scored worse on attention than those with AD among those with CDR = 0, and there were no other statistically significant differences when comparing individuals with possible PART and AD.

Multivariable analyses stratifying by Braak stages (I–II, III–IV) instead of controlling for it are presented in Tables 4 and 5. New findings emerged through stratification. Focusing on Braak stages III–IV, CDR = 0 individuals with definite PART demonstrated a sparing of semantic memory/language compared to CDR = 0 individuals with AD (Table 4), and CDR = 0.5–1 individuals with definite PART demonstrated a sparing of executive function compared to CDR 0.5–1 individuals with AD (Table 5). Stratification revealed that the findings for sparing of global cognition, episodic memory, and semantic memory/language among definite PART individuals with CDR = 0.5–1 in the main analyses (Table 3) were restricted to those with Braak stages III–IV (Table 5).

In post hoc analyses, we found that definite PART participants scored significantly better on all 3 semantic memory/language tests compared to AD participants (Table 6; Fig. 4). However, in the CDR = 0.5–1 and CDR = 2–3 groups, the biggest differences between these 2 groups were observed for the Boston Naming Test. In the sensitivity analysis redefining definite PART based on diffuse plaques instead of NP, the overall results remained similar except that individuals with definite PART (n = 148) scored significantly better than those

with AD in the attention and executive function domains (Supplementary Data Table S3). Lastly, in the sensitivity analyses examining the independent contribution of VBI to cognitive domain scores, we found that among those with CDR = 0, those with VBI scored worse than those without VBI on the global composite, attention, and executive domains (data not shown). In addition, among those with CDR = 0.5 or 1, individuals with VBI scored worse in the attention and executive domains, and no differences were observed between those with and without VBI among individuals with CDR = 2 or 3.

DISCUSSION

We sought to compare antemortem neuropsychological profiles between individuals who at autopsy had PART or AD, and to examine how differences between these groups alter when stratified by disease stage. We found that even within the same stratum of CDR scores, individuals with PART had relative sparing of semantic memory/language in comparison to AD. In addition, when comparing individuals with PART to AD, episodic memory was relatively spared in the moderately severe stratum (CDR 0.5–1) and attention was relatively spared in the most severe stratum (CDR 2–3). Within the asymptomatic stratum there were no differences between PART and AD. Minimal differences in neuropsychological scores were observed when comparing possible PART and AD. It is important to note that individuals in this transitional

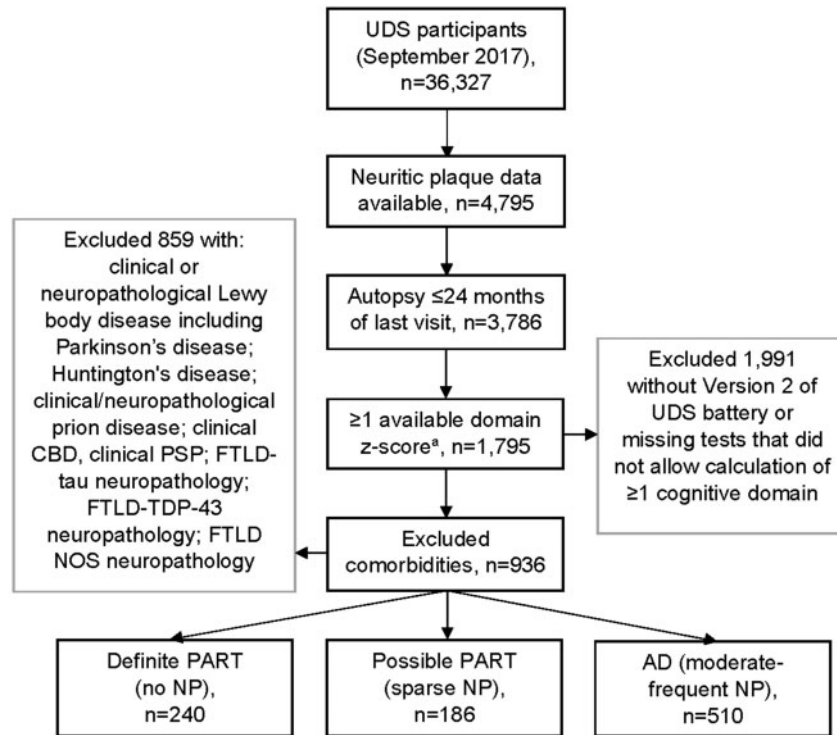


FIGURE 1. Sample selection flow diagram. Over 60% of all 3 neuropathologic groups with CDR = 2 or 3 had missing executive function z-scores. Negative z-scores = scored worse than UDS norms sample mean score; positive z-scores = scored better than UDS norms sample mean score. ^aNonmissing domain based on Version 2 of the UDS neuropsychological test battery. UDS, Uniform Data Set; CBD, corticobasal degeneration; PSP, progressive supranuclear palsy; FTL, frontotemporal lobar degeneration; TDP, TAR DNA-binding protein 43; NOS, not otherwise specified; CDR, Clinical Dementia Rating.

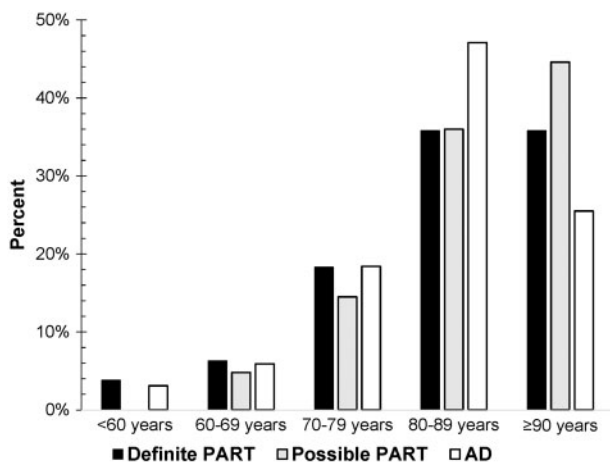


FIGURE 2. Distribution of definite PART, possible PART, and AD sample by age group. For a given neuropathologic group, the sum of the 5 age group percentages equals 100 percent. The majority of the entire sample were 80 years or older. When comparing the 3 neuropathologic groups, a larger proportion of those with AD were 80–89 years old and a larger proportion of the Definite and Possible PART groups were ≥90 years old. PART, primary age-related tauopathy; AD, Alzheimer disease.

category might represent either early AD or, alternatively, resilient individuals who are resistant to further degeneration.

Previous studies suggest that those with PART have less severe cognitive decline than those with AD neuropathologic change (6, 20). This is reinforced by the current study’s finding that more PART participants had CDR = 0 and fewer had CDR = 2–3 in comparison to AD, and the aforementioned findings of relative sparing of semantic memory/language, episodic memory, and attention in PART versus AD. Nonetheless, PART does have cognitive consequences, which are more notable with more advanced pathology. For example, when PART is present, it is more severe (more likely to be Braak stages III/IV) in individuals with mild disease than in asymptomatic individuals (1). In addition, increasing Braak stage has been associated with an increased odds of having a CDR >0 among individuals with PART (5).

The topic of neuropsychological changes in PART has received minimal attention thus far. Two studies have looked at associations between neuropsychological test scores and PART. One study using longitudinal NACC data found progressive cognitive decline in individuals with PART, in particular for tasks involving episodic memory, processing speed, and semantic memory/language (7). Individuals with higher NFT burden were shown to have more rapid decline in episodic and semantic memory/language, as well as processing

TABLE 3. Adjusted Difference in Cognitive Domains at Last Visit in Primary Age-Related Tauopathy Versus Alzheimer Disease
Adjusted Mean Difference in z-Scores^{a,b} (95% CI)

Cognitive domain ^c	CDR = 0		CDR = 0.5 or 1		CDR = 2 or 3	
	Definite PART Versus AD	Possible PART Versus AD	Definite PART Versus AD	Possible PART Versus AD	Definite PART Versus AD	Possible PART Versus AD
Global composite	0.07 (−0.08, 0.21)	−0.03 (−0.19, 0.13)	0.36* (0.08, 0.64)	0.20 (−0.06, 0.46)	0.49 (−0.09, 1.07)	0.33 (−0.30, 0.95)
Episodic memory	0.21 (−0.02, 0.44)	0.15 (−0.07, 0.36)	0.61** (0.39, 0.84)	0.32 (−0.05, 0.68)	0.40 (−0.13, 0.93)	0.11 (−0.25, 0.47)
Attention	0.11 (−0.15, 0.37)	−0.22* (−0.40, −0.04)	0.27 (−0.06, 0.60)	0.15 (−0.14, 0.43)	0.76* (0.09, 1.43)	−0.08 (−0.53, 0.36)
Executive function	−0.09 (−0.36, 0.18)	−0.01 (−0.28, 0.27)	0.28 (−0.13, 0.68)	0.23 (−0.13, 0.59)	0.29 (−0.80, 1.37)	0.59 (−0.82, 2.01)
Semantic memory/ language	0.08 (−0.06, 0.21)	−0.18 (−0.43, 0.07)	0.37** (0.16, 0.58)	0.16 (−0.10, 0.42)	0.92* (0.22, 1.63)	0.23 (−0.24, 0.71)

Abbreviations: CDR, Clinical Dementia Rating; PART, primary age-related tauopathy; AD, Alzheimer disease; CI, confidence interval; vs, versus.

*Statistically significant at $p < 0.05$.

**Statistically significant at $p < 0.01$.

^aControlling for age at last visit, sex, education (years), presence of at least 1 *APOE* $\epsilon 4$ allele; family history of cognitive impairment; history of: hypertension, stroke, diabetes, traumatic brain injury, Braak stage.

^bNegative mean difference in z-scores = scored worse than those with moderate to frequent neuritic plaques; positive mean difference in z-scores = scored better than those with moderate to frequent neuritic plaques.

^cFor all tests but Trail Making Parts A and B, lower score is worse score; therefore Trail Making Part A and B scores (within the executive function domain) were multiplied by -1 to make them consistent with the other tests.

Bold = statistically significant at $p < 0.05$.

speed/attention. There was also a difference between those with definite and possible PART. Unlike the former, with increasing Braak stage, the latter had a faster rate of decline for delayed recall and global impairment on the MMSE. Another study showed that among individuals with PART, there was an association between higher Braak NFT stage and poorer performance on WAIS R Block Design and Trail Making Tests (8).

This study adds to the literature by providing details on the specific neuropsychological domains that are spared in PART versus AD, which has been nominally investigated to date. Moreover, this study adds evidence to the ongoing debate about whether temporal lobe NFTs in the absence of amyloid deposits are necessarily on the AD spectrum (21, 22) or part of an alternative pathway (6, 23). The observed differential pattern of neuropsychological change in PART in comparison to AD provides further evidence that PART might have a distinct trajectory and pathogenesis. In contradistinction, the pattern of neuropsychological change was virtually identical for individuals with possible PART in comparison to AD, suggesting that unlike individuals with definite PART, those with possible PART may not be easily distinguished from AD based on cognitive testing. However, this inability to distinguish the 2 groups clinically does not allow any conclusions about the underlying biologic processes. An individual with sparse amyloid and tauopathy might be on either the AD or PART pathway, or some hybrid thereof. Likewise, individuals with sparse amyloid and tauopathy might represent early AD or alternatively resilience. Other factors, such as genetics or environmental exposure, may also differ among individuals with possible PART and AD. Of note, the differences in cognitive domain scores between the groups did not follow a specific additive pattern. This further reinforces the hypothesis that AD and PART are different pathologic entities with dif-

ferent trajectories rather than different speeds of progression along the same trajectory.

Another study examined MRIs for individuals with PART and found that the posterior but not anterior hippocampus was relatively spared from atrophy (8). The authors suggested that the pattern of atrophy observed in PART, affecting only the anterior hippocampus, may be similar to patterns previously observed in semantic dementia, which is characterized cognitively by deficits in naming and word comprehension with relative preservation of episodic memory and other cognitive domains (24). However, they did not investigate this hypothesis further, but instead proposed that future studies should examine differences in NFT distribution between individuals with PART and AD. In contrast, our study found that semantic memory/language was relatively preserved in PART compared to AD, which is inconsistent with their hypothesis. To help elucidate how differences in anatomic distribution and burden of NFT may affect expression of cognitive symptoms differently in PART and AD, future studies are needed to examine differences in atrophy on MRIs and NFT burden on neuropathological exam by brain region.

Our study has some limitations, including potential residual confounding by disease severity within the CDR strata. Among those in the CDR = 0.5–1 stratum, there were relatively fewer individuals with CDR = 1 in PART (39%) than AD (52%). However, the possible PART group had even fewer (32%) and within the CDR = 2–3 stratum, all 3 neuropathologic groups had similar percentages with CDR = 3 (25%–36%). Hence, this is unlikely to explain the differences in neuropsychologic test scores. Moreover, limitations of sample size did not allow narrower categories and similar concerns would apply if the groups were defined by clinical diagnosis. In addition, although we interpreted significant results at an alpha level of 0.05, this is a limitation due to

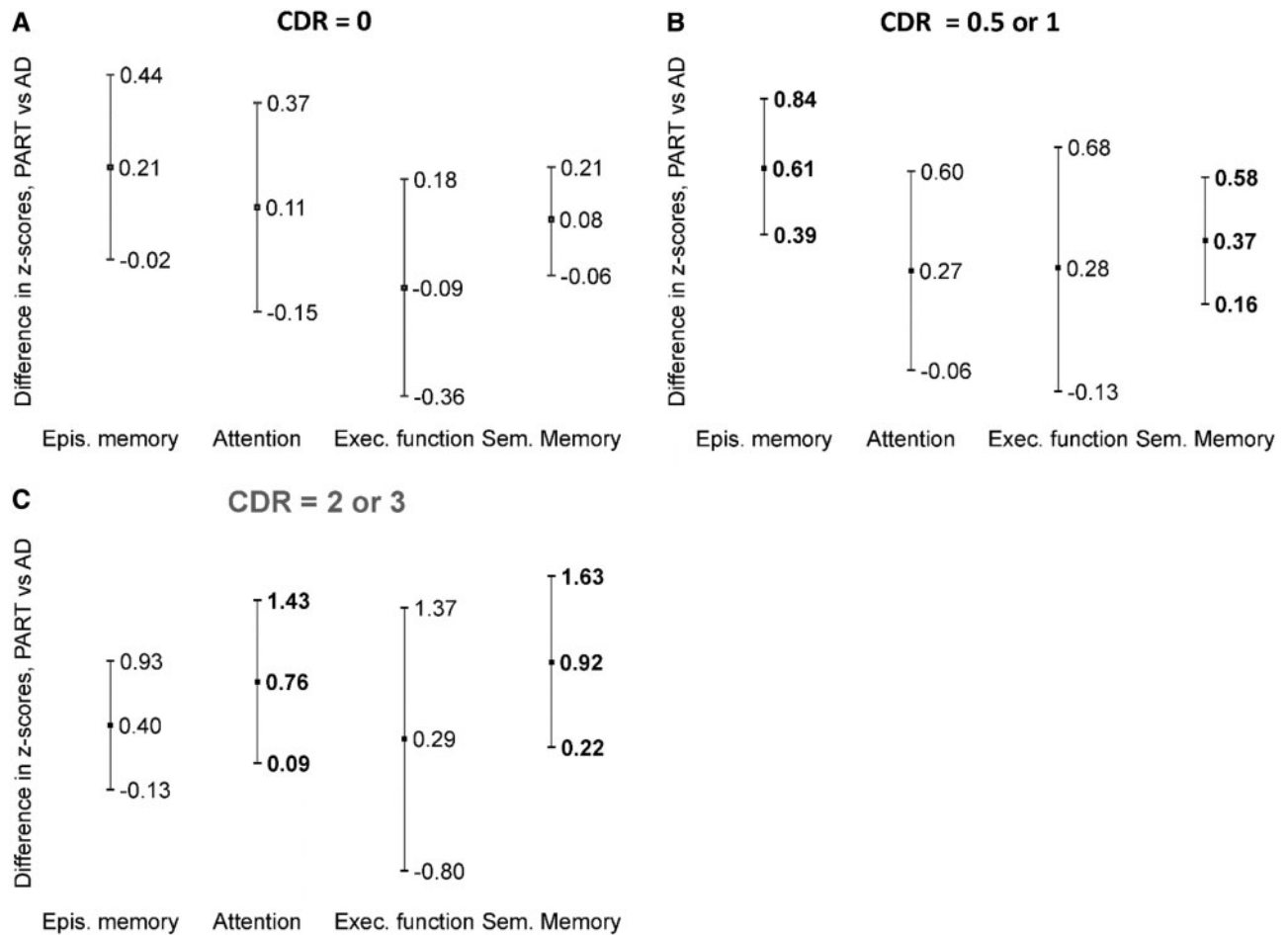


FIGURE 3. Cognitive domain score differences between definite PART and AD by CDR. Estimates (center marker) and upper and lower 95% confidence intervals are presented. Statistically significant differences ($p < 0.05$) are bolded. **(A)** No significant differences between definite PART and AD among those with CDR = 0. **(B)** Among those with CDR = 0.5 or 1, individuals with definite PART scored better than those with AD on tests of episodic memory and semantic memory. **(C)** Among those with CDR = 2 or 3, individuals with definite PART scored better than those with AD on tests of attention and semantic memory. PART, primary age-related tauopathy; AD, Alzheimer disease; CDR, Clinical Dementia Rating; Epis., episodic; Exec, executive.

TABLE 4. Adjusted Difference in Cognitive Domains at Last Visit Among Individuals With CDR = 0

Cognitive domain ^c	Adjusted Mean Difference in z-Scores ^{a,b} (95% CI)			
	Braak Stages I–II		Braak Stages III–IV	
	Definite PART Versus AD	Possible PART Versus AD	Definite PART Versus AD	Possible PART Versus AD
Global composite	-0.01 (-0.20, 0.18)	0.01 (-0.22, 0.24)	0.23 (-0.10, 0.56)	-0.12 (-0.39, 0.16)
Episodic memory	-0.06 (-0.56, 0.44)	-0.01 (-0.52, 0.50)	0.56 (-0.02, 1.14)	0.29*(0.00, 0.58)
Attention	0.10 (-0.22, 0.41)	-0.17 (-0.52, 0.17)	0.08 (-0.35, 0.51)	-0.35*(-0.69, -0.01)
Executive function	-0.12 (-0.36, 0.11)	0.19 (-0.09, 0.46)	-0.18 (-0.68, 0.32)	-0.39 (-0.83, 0.06)
Semantic memory/language	-0.01 (-0.22, 0.19)	-0.22 (-0.56, 0.12)	0.37*(0.08, 0.66)	-0.04 (-0.29, 0.21)

Abbreviations: CDR, Clinical Dementia Rating; NP, neuritic plaques; CI, confidence interval; vs, versus; NA, too few with Braak.

^aStatistically significant at $p < 0.05$.

^bControlling for age at last visit, sex, education (years), presence of at least 1 *APOE* $\epsilon 4$ allele; family history of cognitive impairment; history of: hypertension, stroke, diabetes, traumatic brain injury.

^cNegative mean difference in z-scores = scored worse than those with moderate to frequent neuritic plaques; positive mean difference in z-scores = scored better than those with moderate to frequent neuritic plaques.

^dFor all tests but Trail Making Parts A and B, lower score is worse score; therefore Trail Making Part A and B scores (within the executive function domain) were multiplied by -1 to make them consistent with the other tests.

Bold = statistically significant at $p < 0.05$.

TABLE 5. Adjusted Difference in Cognitive Domains at Last Visit Among Individuals With CDR = 0.5 or 1

Cognitive domain ^c	Adjusted Mean Difference in z-Scores ^{a,b} (95% CI)			
	Braak Stages I–II		Braak Stages III–IV	
	Definite PART Versus AD	Possible PART Versus AD	Definite PART Versus AD	Possible PART Versus AD
Global composite	0.30 (–0.17, 0.76)	0.44 (–0.30, 1.17)	0.48** (0.15, 0.82)	0.10 (–0.32, 0.51)
Episodic memory	0.29 (–0.27, 0.84)	–0.19 (–0.92, 0.54)	0.60** (0.15, 1.06)	0.22 (–0.41, 0.85)
Attention	0.30 (–0.21, 0.80)	0.04 (–0.38, 0.46)	0.23 (–0.16, 0.62)	0.08 (–0.25, 0.42)
Executive function	0.20 (–0.40, 0.80)	1.17* (0.11, 2.22)	0.57* (0.03, 1.11)	0.04 (–0.36, 0.44)
Semantic memory/language	–0.02 (–0.59, 0.54)	–0.13 (–0.61, 0.34)	0.41* (0.04, 0.78)	0.14 (–0.22, 0.51)

Abbreviations: CDR, Clinical Dementia Rating; NP, neuritic plaques; CI, confidence interval; vs, versus.
 *Statistically significant at p < 0.05.
 **Statistically significant at p < 0.01.
^aControlling for age at last visit, sex, education (years), presence of at least 1 *APOE* ε4 allele; family history of cognitive impairment; history of: hypertension, stroke, diabetes, traumatic brain injury.
^bNegative mean difference in z-scores = scored worse than those with moderate to frequent neuritic plaques; positive mean difference in z-scores = scored better than those with moderate to frequent neuritic plaques.
^cFor all tests but Trail Making Parts A and B, lower score is worse score; therefore Trail Making Part A and B scores (within the executive function domain) were multiplied by –1 to make them consistent with the other tests.
 Bold = statistically significant at p < 0.05.

TABLE 6. Adjusted Difference in Semantic Memory/Language at Last Visit in Primary Age-Related Tauopathy Versus Alzheimer Disease

Cognitive test	Adjusted Mean Difference in z-Scores ^{a,b} (95% CI)					
	CDR = 0		CDR = 0.5 or 1		CDR = 2 or 3	
	Definite PART Versus AD	Possible PART Versus AD	Definite PART Versus AD	Possible PART Versus AD	Definite PART Versus AD	Possible PART Versus AD
Animals	–0.06 (–0.25, 0.14)	–0.08 (–0.36, 0.19)	0.27** (0.08, 0.47)	0.14 (–0.03, 0.31)	0.65** (0.24, 1.05)	0.26* (0.00, 0.51)
Vegetables	0.19* (0.02, 0.35)	0.03 (–0.23, 0.30)	0.39** (0.19, 0.59)	0.28** (0.10, 0.45)	0.66** (0.25, 1.07)	0.13 (–0.24, 0.51)
Boston Naming Test	0.11 (–0.11, 0.33)	–0.40** (–0.69, –0.10)	0.53** (0.21, 0.85)	0.19 (–0.35, 0.73)	1.69* (0.14, 3.24)	0.27 (–0.56, 1.10)

Abbreviations: CDR, Clinical Dementia Rating; PART, primary age-related tauopathy; AD, Alzheimer disease; CI, confidence interval; vs, versus.
 *Statistically significant at p < 0.05.
 **Statistically significant at p < 0.01.
^aControlling for age at last visit, sex, education (years), presence of at least 1 *APOE* ε4 allele; family history of cognitive impairment; history of: hypertension, stroke, diabetes, traumatic brain injury, Braak stage.
^bNegative mean difference in z-scores = scored worse than those with moderate to frequent neuritic plaques; positive mean difference in z-scores = scored better than those with moderate to frequent neuritic plaques.
 Bold = statistically significant at p < 0.05.

multiple comparisons. To help address that concern, we also presented associations significant at p < 0.01, finding that individuals with definite PART performed statistically significantly better than those with AD on the episodic memory and semantic memory/language, in those with CDR = 0.5 or 1.

Study participants were more likely to be white and highly educated than the general population, which limits generalizability of the findings. Seventy-four percent were ≥80 years old. Thus, the results may not generalize to younger individuals, although PART is typically considered a neurodegenerative condition affecting older ages (i.e. ≥80 years), and the age distribution was similar between those with definite PART and AD. In addition, data were missing for some of the neuropsychological tests. Typically, ≤10% of the data were missing across domains and missingness was generally similar for the neuropathologic groups. A ma-

ior exception was that although the neuropathologic groups had similar levels of missingness of executive function scores, the percent missing by neuropathologic group was much higher for this domain than other domains (range: 13%–75%). However, missing data is unlikely to have substantially affected our main findings regarding episodic memory, attention, and semantic memory/language. The relative sparing of attention in PART participants with CDR >0 may be explained by the limited tests measuring attention in UDS neuropsychological battery or residual confounding by unreported vascular disease (which affects attention) due to the self-reported nature of the stroke and hypertension control variables.

PART was defined based on CERAD NP, which is not synonymous with amyloid plaques, and future studies of PART will need to assess whether CERAD NP are an adequate substitute. In our sensitivity analysis of definite PART,

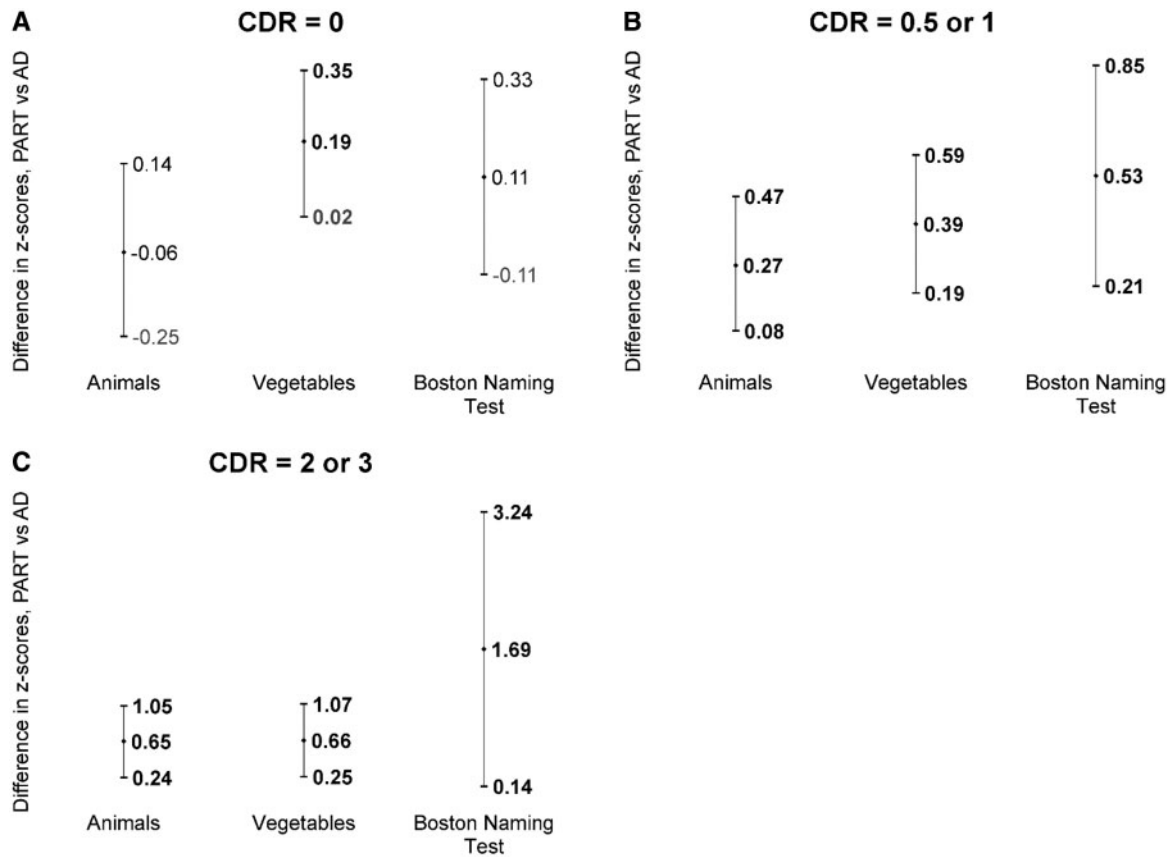


FIGURE 4. Semantic language/memory test score differences between definite PART and AD by CDR. Estimates (center marker) and upper and lower 95% confidence intervals are presented. Statistically significant differences ($p < 0.05$) are bolded. **(A)** Among those with CDR = 0, individuals with definite PART scored better than those with AD on the Vegetables List Generation test. **(B)** Among those with CDR = 0.5 or 1, individuals with definite PART scored better than those with AD on the Animals and Vegetables List Generation tests and on the Boston Naming Test. **(C)** Among those with CDR = 2 or 3, individuals with definite PART scored better than those with AD on the Vegetables List Generation test. PART, primary age-related tauopathy; AD, Alzheimer disease; CDR, Clinical Dementia Rating.

substituting the absence of diffuse plaques (proxy for Thal phase 0) for the absence of CERAD NP, the overall findings remained similar to the main analyses, but suggested that those with no diffuse plaques also performed better than those with AD in 2 additional domains (executive function and attention). Future studies will be needed to determine if these results hold when PART is defined using Thal phase. In addition, individuals with PART more frequently had lower Braak stages and individuals with AD more frequently had higher Braak stages, leading to potential limitations in the comparisons. However, we accounted for Braak NFT stage to the extent possible in our analyses.

We applied a number of exclusions in this study to help assure that we were assessing PART, not other pathologies. VBI at autopsy was not excluded due to its high prevalence in the sample, and a sensitivity analysis indicated that PART and VBI independently contributed to differences in cognition. As PART becomes better characterized in the literature, future studies examining PART with and without additional copathologies will be of increasing interest.

Despite these limitations, this study has major strengths. It provides multi-institutional data on a large group of individuals who had PART or AD, identified by neuropathological exam at autopsy using standardized techniques. It is one of the first studies to compare scores from a battery of standardized neuropsychological tests between individuals with either autopsy-confirmed PART or autopsy-confirmed AD. In addition, this study allows us to draw reasonable conclusions about the pattern of neuropsychological changes at several stages of PART.

Our study confirms prior studies showing that PART is less likely to be associated with more severe dementia than is AD. Within the same stratum of CDR scores, PART was associated with a different pattern of neuropsychological change than AD, with relative sparing of semantic memory/language among those with any cognitive impairment, and in the most severe stratum, with additional sparing of attention. The relatively small observed differences in cognitive domain scores suggests that more sensitive neuropsychological tests or biomarkers/neuroimaging may be better suited to clinically distinguish PART from AD during life. Nonetheless, the study adds further evidence for

the hypothesis that PART is a distinct pathologic entity, with different biologic consequences than AD.

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