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Cognitive Decline Associated with Pathological Burden in Primary Age-Related Tauopathy

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Abstract

INTRODUCTION—Primary age-related tauopathy (PART) is a neuropathological diagnosis characterized by neurofibrillary tau tangles (NFTs) in the absence of amyloid plaque pathology. While most individuals over 50 years of age have evidence of NFTs, the clinical and cognitive consequences of PART are not known.

METHODS—We evaluated 226 neuropathologically-confirmed PART cases from the National Alzheimer’s Coordinating Center database who participated in a total of 846 longitudinal neuropsychological assessments from the Alzheimer’s Disease Center program’s Uniform Data Set. Mixed-effects statistical models tested whether cognitive decline was associated with Braak stage NFT burden.

RESULTS—Higher stages of NFT burden in PART, with no evidence or minimal evidence of amyloid pathology, were associated with more rapid decline on tasks involving episodic and semantic memory along with tests of processing speed and attention.

DISCUSSION—We conclude that PART has cognitive consequences that should be considered in the context of emerging tau-targeted therapies in age-associated neurodegenerative diseases.

Keywords

primary age-related tauopathy; tau; cognition; clinical prognosis

Alzheimer’s Disease (AD) is neuropathologically-characterized by the presence of both tau neurofibrillary tangles (NFTs) and amyloid beta plaques (A β)[1], yet autopsy studies have identified a subset of individuals who have NFTs in the absence of A β . Recently the term

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Conflicts of Interest. Nothing to Report

primary age-related tauopathy (PART) was coined to describe this condition,[7] defined by neuropathological criteria of the presence of predominately limbic NFT pathology up to Braak stage IV.[8] PART is further defined as “Definite” with no evidence of neuritic plaque density or “Possible” with minimal evidence of neuritic plaques.[7] However, criteria for the diagnosis of PART are strictly neuropathological and little is known about the cognitive manifestations associated with PART.

Historically, when associated with dementia, PART was previously termed tangle-predominant senile dementia[2] or senile dementia of the neurofibrillary tangle type.[3] However, NFTs in the absence of A β pathology are also quite common in cognitively normal elderly individuals[4,5] with most individuals over the age of 50 having some level of tau inclusions.[6] Therefore, since PART can be associated with dementia or normal cognition in aging adults, it is necessary to evaluate the direct influence of NFT burden on cognition in a pathologically, rather than clinically, defined cohort. While it has been demonstrated that Mini Mental State Examination (MMSE) is correlated with increased NFT burden in PART[7] more detailed and longitudinal clinical data have not been characterized. This cohort study therefore aims to identify the longitudinal cognitive consequences of PART and identify whether cognitive decline is associated with increases in NFT burden in the absence of amyloid pathology.

Methods

Study Population

Neuropathological and neuropsychological data were obtained for all individuals over 50 years old at death from the National Alzheimer’s Coordinating Center (NACC) database, and we report data from 32 past and present Alzheimer’s Disease Centers (ADCs). All participants completed a neuropsychological assessment from the Uniform Data Set (UDS), described in detail elsewhere[9] and summarized in Table 1. We also evaluated the frequency of clinically-detected cognitive impairment using a clinician’s rating of “impaired” or “cognitively normal” obtained from the UDS.

To define neuropathological groups we queried Braak stage and neuritic plaque ratings available in the NACC neuropathological database. These ratings are performed using independent methods (e.g., PHF-1, Thioflavin-S, Silver staining) by trained neuropathologists from each participating ADC, but despite heterogeneous methods there is established excellent agreement in ratings across sites.[10] We then selected the subset of individuals with neuropathological evidence of NFTs consistent with Braak stage I/II or III/IV[8]. For each Braak stage group we classified each individual as having “Definite” (CERAD=0) or “Possible” (CERAD=1) PART using published criteria.[7] To focus exclusively on PART, we excluded individuals who met primary or secondary neuropathological criteria for a related neurodegenerative disease such as frontotemporal degeneration (e.g., tau, TDP-43, or FUS) or a Lewy body disorder (e.g., alpha-synuclein). This yielded 226 unique subjects who participated in a total of 846 neuropsychological assessments between September 2005 and June 2015. On average individuals participated in 3.97 (SD=1.84) neuropsychological assessments and 70% of individuals participated in 3 or more neuropsychological assessments.

Statistical analysis

We evaluated demographic, clinical, and neuropsychological characteristics at baseline and final assessment using group-wise comparisons across the four neuropathological groups: Definite PART I/II, Definite PART III/IV, Possible PART I/II, and Possible PART III/IV. Chi-square analyses were used for categorical subject characteristics and non-parametric Kruskal-Wallis tests were used to evaluate continuous measures. Post hoc comparisons were performed using Wilcoxon and Mann-Whitney non-parametric tests. These exploratory analyses accepting a $p < 0.05$ were not corrected for multiple statistical comparisons.

To evaluate longitudinal decline we performed linear mixed-effect regression analyses using the *nlme* package in R [11] across the entire cohort. For fixed effects, we represent time as the numbers of years between testing date and death, Braak stage, neuritic plaque burden, and an interaction term of Time \times Braak stage \times Neuritic Plaque Burden. We focus our results on the latter three-way interaction term to evaluate the influence of Braak stage and time within each PART group (Definite, Possible). We also included covariates of education level, age at death, and sex. For random effects, we included intercepts for subjects to account for variation between individuals.

Results

Group-wise comparisons of demographics (see Table 1) revealed differences in sex, frequency of clinically-detected cognitive impairment, and differences in age at baseline assessment, final assessment, and death. All groups were comparable for education and frequency of visits (all $p < 0.1$). Post hoc pairwise comparisons are summarized in Table 1. We observed that individuals with Braak stage III/IV are older and more frequently diagnosed with cognitive impairment relative to individuals with Braak stage I/II pathology (all $p < 0.001$). We also observed a lower proportion of females in the Possible PART I/II relative to the Possible PART III/IV group ($p < 0.05$). All other post hoc comparisons were not significant suggesting that demographic characteristics do not vary with presence (Possible PART) or absence (Definite PART) of amyloid pathology.

Group-wise comparisons of baseline and final neuropsychological assessments (see Table 1) revealed differences in performance on the Trails-B, WAIS Digit-Symbol, and Boston Naming Test. At final assessment we also observed group-wise differences in Trails-A performance. Post hoc analyses are summarized in Table 1. Notably, among all pairwise comparisons the significant results (all $p < 0.05$) were related to more impaired performance for Braak III/IV patients relative to Braak I/II patients in either the Definite or Possible PART groups. The only observed difference associated with amyloid-defined pathological groups was for Trails-B in which Possible PART III/IV cases were more impaired than Definite PART III/IV cases.

Longitudinal analyses are summarized in Table 2. We observed significant three-way interactions of Time \times Braak stage for both the Definite PART and Possible PART groups on tests of Category Fluency, Logical Memory Immediate Recall, WAIS Digit-Symbol, and Trails-A (see Supplemental Figure 1). A Time \times Braak stage interaction was also observed for the Possible PART group on MMSE and Logical Memory Delayed, but not the Definite

PART group. Time X Braak stage interactions were not observed for either PART group on Digit Span Backwards or Boston Naming Test. Notably, the main effect for amyloid neuritic plaque burden was only significant for Category Fluency.

Discussion

Our results provide longitudinal evidence suggesting that PART, a neuropathologically-defined condition, has clinical consequences that include a progressive cognitive decline in tasks involving memory, processing speed, and attention. The medial temporal lobes are known to have early NFT deposition in Braak staging[12] and be critical to episodic memory. Moreover, given that difficulty on later trials of immediate delayed recall has been associated with medial temporal lobe and temporal pole disease[13], it is not surprising that Braak stage III/IV is associated with more severe decline in immediate memory performance for individuals with PART.

Our observation that semantic memory was affected in the Category Fluency task is also consistent with temporal lobe involvement,[14] including regions that have Braak stage III/IV pathology.[8] Recently it has been suggested that the medial perirhinal cortex, the first region of NFT deposition (Braak stage I)[8], is important in object-related semantic knowledge, particularly for “living items” such as animals, and atrophy in this region correlates with category fluency and naming.[15] While longitudinal decline in naming performance was not associated with Braak stage, naming performance was impaired at baseline and final assessment for individuals with Braak III/IV relative to Braak stage I/II. Collectively, these findings along with immediate delayed recall decline implicate a critical role for temporal lobe involvement in the cognitive difficulties observed in individuals meeting neuropathological criteria for PART.

Tasks testing visuomotor speed and sequencing, Trails-A and WAIS Digit-Symbol, are typically associated dorsal frontal or fronto-parietal control regions.[16,17] However, Braak stage III/IV does not involve these regions and therefore it is not clear why we observed more rapid decline in these domains. Future work will need to determine the degree to which the regional distribution of PART is associated with domain-specific processing-speed/attention performance or more general cognitive function, which would likely have implications for the mechanism of dysfunction in this condition.

Further investigation is required to determine whether PART is a unique neuropathological condition, reflects membership in the spectrum of AD, or is a result of the pathological consequences of aging.[18] Critically, we observed significant cognitive decline and a higher frequency of clinically-detected cognitive impairment associated with higher burden of NFTs in both the Possible and Definite PART cases. Also, given our observation that, independent of amyloid burden, Braak stage III/IV is associated with older age than Braak stage I/II, it is possible that PART is a unique neuropathological condition and an important contributor to age-related cognitive decline. We did, however, observe that relative to Definite PART cases, there was a steeper rate of cognitive decline in Possible PART cases that extended to include delayed recall and global impairment on the MMSE. Thus, while the current data suggests that cognitive decline is associated with higher NFT burden in both

groups, we cannot rule out the possibility that Possible PART cases are following a trajectory toward the development of intermediate AD pathology.

Caveats to consider are the multi-center and retrospective nature of this cohort study. Recruitment methods across ADCs vary and therefore this cohort may not be representative of the larger population. Also there could be heterogeneity in neuropathologists' ratings of Braak stages and neuritic plaque scores; however, these neuropathological criteria were recently validated in a multicenter center study with high inter-rater agreement.[10] Given that there could still be inconsistencies across sites leading to diagnostic "error" (e.g., calling an AD case "possible" PART), we performed *post hoc* analyses (not reported) including ADC site as a covariate and this did not influence any of the reported associations of Braak stage and neuritic plaque scores. Ideally we would evaluate a neuropathological control group with sparing of both NFTs and neuritic plaques; however, the absence of both forms of pathology is extraordinarily rare (only 13 individuals from our NACC query were lacking distinctive pathology with available longitudinal neuropsychological data). While we excluded individuals with alternative sources of neuropathological burden that met a secondary neuropathological diagnosis (e.g., TDP-43 or alpha-synuclein), these sources of proteinopathy are known to also accumulate in the aging brain.[19] Likewise, while our clinical observations appeared to be uniquely related to NFT and not amyloid burden, it would be valuable for future studies of Possible PART to evaluate whether regional distribution of amyloid, Thal phase, influences cognition. However, alpha-synuclein and TDP-43 pathological burden level and amyloid Thal phase have only recently been recorded in the NACC dataset. It is also possible that earliest loci of tau deposition in the raphe nucleus and locus coeruleus [20,21] that precedes cortical tau deposition may influence early clinical features of PART such as sleep dysfunction, but this regional data also is not available in this pathological case series. Evaluation of these additional neuropathological features will be an important topic for future investigations.

Individuals with PART, independent of the presence of minimal amyloid pathology, exhibit longitudinal cognitive decline that increases in severity with higher levels of NFT pathology. Thus, this evidence suggests that PART has true cognitive consequences that may contribute to age-related cognitive decline and could impact clinical progression seen in other neurodegenerative conditions, including AD. The degree to which PART represents a potential target for therapeutic intervention remains to be determined. Emergent tau-PET imaging techniques may enhance our ability to study this condition *in vivo* to address these questions.[22] Furthermore, future investigations are necessary to identify alternative candidate biomarkers, such as cerebrospinal fluid or magnetic resonance imaging, to identify individuals with PART during life and evaluate whether these individuals may serve as candidates for emerging therapeutic approaches targeting misfolded tau inclusions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR, Kawas CH, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 2011; 7:263–9. DOI: 10.1016/j.jalz.2011.03.005 [PubMed: 21514250]
2. Jellinger KA, Attems J. Neurofibrillary tangle-predominant dementia: comparison with classical Alzheimer disease. *Acta Neuropathol*. 2007; 113:107–17. DOI: 10.1007/s00401-006-0156-7 [PubMed: 17089134]
3. Yamada M. Senile dementia of the neurofibrillary tangle type (tangle-only dementia): neuropathological criteria and clinical guidelines for diagnosis. *Neuropathology*. 2003; 23:311–7. [PubMed: 14719548]
4. Knopman DS, Parisi JE, Salviati A, Floriach-Robert M, Boeve BF, Ivnik RJ, et al. Neuropathology of cognitively normal elderly. *J Neuropathol Exp Neurol*. 2003; 62:1087–95. [PubMed: 14656067]
5. Bennett DA, Schneider JA, Arvanitakis Z, Kelly JF, Aggarwal NT, Shah RC, et al. Neuropathology of older persons without cognitive impairment from two community-based studies. *Neurology*. 2006; 66:1837–44. DOI: 10.1212/01.wnl.0000219668.47116.e6 [PubMed: 16801647]
6. Bouras C, Hof PR, Morrison JH. Neurofibrillary tangle densities in the hippocampal formation in a non-demented population define subgroups of patients with differential early pathologic changes. *Neurosci Lett*. 1993; 153:131–5. [PubMed: 8327187]
7. Crary JF, Trojanowski JQ, Schneider JA, Abisambra JF, Abner EL, Alafuzoff I, et al. Primary age-related tauopathy (PART): a common pathology associated with human aging. *Acta Neuropathol*. 2014; 128:755–66. DOI: 10.1007/s00401-014-1349-0 [PubMed: 25348064]
8. Braak H, Braak E. Staging of Alzheimer's disease-related neurofibrillary changes. *Neurobiology of Aging*. 1995; 16:271–8. discussion 278–84. [PubMed: 7566337]
9. Weintraub S, Salmon D, Mercaldo N, Ferris S, Graff-Radford NR, Chui H, et al. The Alzheimer's Disease Centers' Uniform Data Set (UDS): the neuropsychologic test battery. *Alzheimer Dis Assoc Disord*. 2009; 23:91–101. DOI: 10.1097/WAD.0b013e318191c7dd [PubMed: 19474567]
10. Montine TJ, Monsell SE, Beach TG, Bigio EH, Bu Y, Cairns NJ, et al. Multisite assessment of NIA-AA guidelines for the neuropathologic evaluation of Alzheimer's disease. *Alzheimers Dement*. 2016; 12:164–9. DOI: 10.1016/j.jalz.2015.07.492 [PubMed: 26327235]
11. Pinheiro, J., Bates, D., Debroy, S., Sarkar, D., R Core Team. *nlme: Linear and Nonlinear Mixed Effects Models*. 3rd. 2016.
12. Braak H, Braak E. Neuropathological staging of Alzheimer-related changes. *Acta Neuropathol*. 1991; 82:239–59. [PubMed: 1759558]
13. Wolk DA, Dickerson BC, Alzheimer's Disease Neuroimaging Initiative. Fractionating verbal episodic memory in Alzheimer's disease. *NeuroImage*. 2011; 54:1530–9. DOI: 10.1016/j.neuroimage.2010.09.005 [PubMed: 20832485]

14. Zhang H, Sachdev PS, Wen W, Kochan NA, Crawford JD, Brodaty H, et al. Grey matter correlates of three language tests in non-demented older adults. *PLoS ONE*. 2013; 8:e80215.doi: 10.1371/journal.pone.0080215 [PubMed: 24224044]
15. Clarke A, Tyler LK. Understanding What We See: How We Derive Meaning From Vision. *Trends Cogn Sci (Regul Ed)*. 2015; 19:677–87. DOI: 10.1016/j.tics.2015.08.008 [PubMed: 26440124]
16. Wolk DA, Dickerson BC, Alzheimer's Disease Neuroimaging Initiative. Apolipoprotein E (APOE) genotype has dissociable effects on memory and attentional-executive network function in Alzheimer's disease. *Proceedings of the National Academy of Sciences*. 2010; 107:10256–61. DOI: 10.1073/pnas.1001412107
17. Usui N, Haji T, Maruyama M, Katsuyama N, Uchida S, Hozawa A, et al. Cortical areas related to performance of WAIS Digit Symbol Test: a functional imaging study. *Neurosci Lett*. 2009; 463:1–5. DOI: 10.1016/j.neulet.2009.07.048 [PubMed: 19631255]
18. Jellinger KA, Alafuzoff I, Attems J, Beach TG, Cairns NJ, Crary JF, et al. PART, a distinct tauopathy, different from classical sporadic Alzheimer disease. *Acta Neuropathol*. 2015; 129:757–62. DOI: 10.1007/s00401-015-1407-2 [PubMed: 25778618]
19. Kovacs GG, Milenkovic I, Wöhler A, Höftberger R, Gelpi E, Haberler C, et al. Non-Alzheimer neurodegenerative pathologies and their combinations are more frequent than commonly believed in the elderly brain: a community-based autopsy series. *Acta Neuropathol*. 2013; 126:365–84. DOI: 10.1007/s00401-013-1157-y [PubMed: 23900711]
20. Braak H, Thal DR, Ghebremedhin E, Del Tredici K. Stages of the pathologic process in Alzheimer disease: age categories from 1 to 100 years. *J Neuropathol Exp Neurol*. 2011; 70:960–9. DOI: 10.1097/NEN.0b013e318232a379 [PubMed: 22002422]
21. Grinberg LT, Rüb U, Ferretti REL, Nitrini R, Farfel JM, Polichiso L, et al. The dorsal raphe nucleus shows phospho-tau neurofibrillary changes before the transentorhinal region in Alzheimer's disease. A precocious onset? *Neuropathol Appl Neurobiol*. 2009; 35:406–16. DOI: 10.1111/j.1365-2990.2009.00997.x [PubMed: 19508444]
22. Ossenkoppele R, Schonhaut DR, Schöll M, Lockhart SN, Ayakta N, Baker SL, et al. Tau PET patterns mirror clinical and neuroanatomical variability in Alzheimer's disease. *Brain*. 2016; doi: 10.1093/brain/aww027

RESEARCH IN CONTEXT

Systematic Review

The authors searched PubMed for all papers related to cognition in primary age-related tauopathy (PART). While the neuropathology of PART has recently been defined the cognitive and clinical consequences have not previously been evaluated beyond global cognitive measures (e.g., MMSE).

Interpretation

In a longitudinal analysis we identified that higher stages of neurofibrillary tau tangles (NFTs) in PART are associated with more rapid cognitive decline. We conclude that PART has cognitive consequences that should be considered in the context of emerging therapies targeting tau in age-associated neurodegenerative diseases.

Future Directions

Further investigation is required to determine whether PART is a unique neuropathological condition, reflects membership in the spectrum of AD, or is a result of the pathological consequences of aging.

HIGHLIGHTS

- The clinical consequences of primary age-related tauopathy (PART) are unknown.
- Neurofibrillary tau tangles (NFTs) in PART increase with age.
- Higher levels of NFTs in PART are associated with more rapid cognitive decline.

Table 1

Median [IQR] and frequency summaries of demographics, baseline assessment of neuropsychological performance, and final assessment of neuropsychological performance for 226 individuals with neuropathological confirmation of primary age-related tauopathy (PART).

	Visit	Definite PART I/II	Definite PART III/IV	Possible PART I/II	Possible PART III/IV	p-value
<i>Demographics</i>						
N	-	79	49	39	59	-
Sex, % female	-	48.1%	61.2%	15.9%	64.4% ^c	0.021
Education, years	-	16.0 [12.5–18.0]	15.0 [14.0–18.0]	16.0 [13.0–18.0]	15.0 [12.0–16.5]	0.518
Age at Death, years	-	84.0 [78.0–90.0]	92.0 ^a [88.0–94.0]	86.0 [82.0–91.0]	92.0 ^b [86.0–96.0]	<0.001
Frequency of Visits, quantity	-	3.0 [2.0–5.5]	3.0 [2.0–5.0]	4.0 [3.0–5.0]	3.0 [2.0–5.0]	0.733
Cognitively Impaired, % total	-	37.7%	53.1% ^a	50.0%	69.0% ^b	
<i>Global</i>						
Age, years	Baseline	80.0 [73.0–86.0]	87.0 ^a [84.0–90.0]	82.0 [77.5–85.0]	87.0 ^b [81.0–91.5]	<0.001
	Final	83.0 [77.0–88.5]	90.0 ^a [87.0–93.0]	84.0 [80.5–89.5]	90.0 ^b [85.0–94.5]	<0.001
<i>Executive</i>						
MMSE, total correct	Baseline	28.0 [27.0–30.0]	28.0 [26.0–29.0]	29.0 [27.0–29.5]	28.0 [26.5–29.0]	0.328
	Final	28.0 [26.5–29.0]	28.0 [25.0–29.0]	28.0 [25.5–30.0]	27.0 [26.0–29.0]	0.143
<i>Memory</i>						
Trails-B, completion time	Baseline	105.0 [78.0–150.5]	145.0 ^a [90.0–190.0]	102.0 [82.5–132.0]	131.0 [105.5–184.5]	0.003
	Final	123.0 [85.5–233.5]	164.0 [91.0–252.0]	112.0 [85.5–172.5]	199.0 ^{b,c} [138.5–300.0]	0.001
<i>Logical Memory Immediate, # words</i>						
	Baseline	13.0 [9.5–16.0]	12.0 [7.0–16.0]	13.0 [8.0–15.0]	12.0 [10.0–15.0]	0.518
	Final	14.0 [10.0–17.0]	12.0 [6.0–15.0]	12.0 [4.0–16.5]	11.0 [7.0–15.0]	0.137

Visit	Definite PART I/II	Definite PART III/IV	Possible PART I/II	Possible PART III/IV	p-value
Logical Memory Delayed, # words	Baseline	12.0 [9.5–15.0]	11.0 [7.0–14.0]	11.0 [4.5–14.5]	0.111
	Final	12.0 [8.0–16.0]	10.0 [1.0–15.0]	10.0 [5.0–13.5]	0.092
<i>Processing Speed/Attention</i>					
WAIS Digit-Symbol, correct pairs	Baseline	38.0 [29.8–46.0]	36.0 [28.0–43.0]	37.0 [31.8–45.0]	0.015
	Final	33.0 [26.0–42.0]	31.0 [25.3–42.8]	32.0 [27.0–41.0]	0.008
Trails-A, completion time	Baseline	41.0 [32.0–48.0]	45.0 [32.0–56.0]	42.0 [32.0–54.0]	0.312
	Final	47.0 [33.5–61.0]	48.0 [35.0–74.0]	47.0 [35.3–56.8]	0.043
Digit Span Forward, span length	Baseline	8.0 [7.0–10.5]	8.0 [7.0–9.0]	9.0 [7.0–10.0]	0.34
	Final	8.00 [7.0–9.0]	8.00 [6.0–9.0]	8.00 [7.0–9.0]	0.997
Digit Span Backward, span length	Baseline	7.0 [5.0–8.0]	6.0 [4.0–8.0]	6.0 [5.0–7.0]	0.103
	Final	6.0 [5.0–8.0]	6.0 [4.0–7.0]	6.0 [5.0–7.0]	0.161
<i>Language & Semantic Memory</i>					
Category Fluency, # animal words	Baseline	17.0 [13.0–22.0]	17.0 [12.0–22.0]	17.0 [14.5–21.0]	0.52
	Final	17.0 [11.0–21.0]	15.0 [10.0–20.0]	16.0 [11.5–19.0]	0.065
Boston Naming Test, total correct	Baseline	28.0 [26.0–29.0]	27.0 ^a [24.0–28.0]	27.0 [24.5–28.0]	0.004
	Final	28.0 [25.0–29.0]	27.0 ^a [24.0–28.0]	27.0 [22.5–29.0]	0.015

Note. Significant post hoc differences (all p<0.05):

^a = Definite PART III/IV relative to Definite PART I/II,

^b = Possible PART III/IV relative to Possible PART I/II, and

^c = Possible PART III/IV relative to Definite PART III/IV.

Table 2

Longitudinal linear mixed-effects regression models evaluating cognitive decline in 226 patients with primary age-related tauopathy (PART).

Model Factor	Time		Braak stage		Neuritic Plaques		Time X Braak Definite PART		Time X Braak Possible PART		Age at Test		Education		Sex	
	β	p	β	p	β	p	β	p	β	p	β	p	β	p	β	p
Global Cognition																
MMSE (total correct)	-0.011	0.914	-0.732	0.124	-0.104	0.815	0.105	0.161	0.197	0.003	-0.031	0.267	0.170	0.016	0.566	0.158
Executive																
Trails-B (completion time)	-1.658	0.558	33.414	0.004	12.019	0.267	-3.918	0.060	-5.593	0.002	2.133	0.001	-2.751	0.095	-1.090	0.907
Memory																
Logical Memory – Immediate (# words)	-0.364	0.014	-1.347	0.089	-0.701	0.341	0.243	0.027	0.304	0.002	-0.072	0.128	0.415	0.001	1.724	0.012
Logical Memory – Delayed (# words)	-0.221	0.178	-1.557	0.075	-0.969	0.233	0.145	0.229	0.251	0.018	-0.093	0.075	0.469	0.000	2.074	0.006
Processing Speed/Attention																
WAIS Digit-Symbol (correct pairs)	0.471	0.160	-2.293	0.181	-2.656	0.098	0.527	0.036	0.637	0.004	-0.521	0.000	0.489	0.058	2.031	0.168
Trails-A (completion time)	0.228	0.823	6.432	0.091	3.947	0.266	-1.841	0.014	-1.940	0.003	0.799	0.000	-0.019	0.971	-1.119	0.706
Digits – Forward (span length)	0.255	0.002	-0.040	0.896	-0.410	0.158	-0.147	0.015	-0.056	0.296	-0.009	0.602	0.103	0.016	0.233	0.339
Digits – Backward (span length)	0.045	0.606	-0.874	0.008	-0.577	0.058	0.038	0.550	0.107	0.058	0.005	0.758	0.139	0.002	0.373	0.143
Language & Semantic Memory																
Category Fluency (# animal words)	-0.072	0.725	-1.063	0.231	-1.653	0.047	0.297	0.051	0.425	0.002	-0.125	0.014	0.351	0.006	0.304	0.677
Boston Naming (total correct)	0.255	0.006	-0.219	0.739	-1.043	0.089	-0.100	0.148	-0.023	0.700	-0.045	0.270	0.215	0.038	-0.662	0.264