1 **Title:**

2 **Predictors of cognitive impairment in primary age-related tauopathy: an autopsy study**

3 **Authors:** Megan A. Iida BS^{1*}, Kurt Farrell PhD^{1*}, , Jamie M. Walker MD, PhD², Timothy E. Richardson
4 DO, PhD², Gabe Marx¹, Clare H. Bryce MD¹, Dushyant Purohit MD¹, Gai Ayalon PhD⁴, Thomas G. Beach
5 MD-PhD⁵, Eileen H. Bigio MD⁶, Etty Cortes MD¹, Marla Gearing PhD⁷, Vahram Haroutunian PhD⁸, Corey
6 T. McMillan PhD⁹, Eddie B. Lee⁹, Dennis Dickson MD¹⁰, Ann C. McKee MD¹¹, Thor D. Stein MD-PhD¹¹,
7 John Q. Trojanowski MD-PhD¹², Randall L. Woltjer MD¹³, Gabor G. Kovacs MD-PhD^{14,15,16}, Julia K. Kofler
8 MD¹⁷, Jeffrey Kaye MD¹⁸, Charles L. White III MD¹⁹, John F. Crary MD-PhD^{1**}

9
10 1) Department of Pathology, Neuropathology Brain Bank & Research CoRE, Nash Family Department of
11 Neuroscience, Friedman Brain Institute, Ronald M. Loeb Center for Alzheimer's Disease, Icahn School
12 of Medicine at Mount Sinai, USA;

13
14 2) Department of Pathology and Laboratory Medicine and The Glenn Biggs Institute for Alzheimer's &
15 Neurodegenerative Diseases, UT Health San Antonio, San Antonio, TX, USA;

16
17 4) Ultragenyx Pharmaceuticals USA;

18
19 5) Neuropathology, Banner Sun Health Research Institute, Sun City, Arizona, USA;

20
21 6) Department of Pathology, Northwestern Cognitive Neurology and Alzheimer Disease Center,
22 Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA;

23
24 7) Department of Pathology and Laboratory Medicine, Emory University School of Medicine, Atlanta,
25 Georgia, USA;

26
27 8) Departments of Psychiatry and Neuroscience; Alzheimer's Disease Research Center, Icahn School of
28 Medicine at Mount Sinai, New York, New York, USA; and JJ Peters VA Medical Center (MIRECC), Bronx,
29 NY.

30
31 9) Department of Neurology, Perelman School of Medicine, Penn FTD Center, Center for
32 Neurodegenerative Disease Research, University of Pennsylvania, Philadelphia, Pennsylvania, USA;

33
34 10) Department of Neuroscience, Mayo Clinic, Jacksonville, Florida, USA;

35
36 11) Department of Pathology, VA Medical Center & Boston University School of Medicine, Boston,
37 Massachusetts, USA;

38
39 12) Center for Neurodegenerative Disease Research, Department of Pathology and Laboratory Medicine,
40 Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA;

41
42 13) Department of Pathology, Oregon Health Sciences University, Portland, Oregon, USA;

43
44 14) Laboratory Medicine Program & Krembil Brain Institute University Health Network Toronto Ontario
45 Canada;

46

15) Tanz Centre for Research in Neurodegenerative Disease and Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, Ontario, Canada;

16) Previous address: Institute of Neurology, Medical University of Vienna, Vienna, Austria;

17) Department of Pathology, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, USA;

18) Department of Neurology, Oregon Health & Science University, Portland USA;

19) Neuropathology Laboratory, Department of Pathology, University of Texas Southwestern Medical Center, USA;

* These authors contributed equally to this work

** Correspondence:

John F. Crary, MD-PhD

Professor, Department of Pathology

Director, Neuropathology Brain Bank & Research CoRE

Nash Family Department of Neuroscience

Friedman Brain Institute

Ronald M. Loeb Center for Alzheimer's Disease

Icahn School of Medicine at Mount Sinai

1 Gustave L. Levy Place Box 1194 New York, NY 10029, USA

Telephone: (212) 659-8695, Email: john.crary@mountsinai.org

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Abstract

Primary age-related tauopathy (PART) is a form of Alzheimer-type neurofibrillary degeneration occurring in the absence of amyloid-beta (A β) plaques. While PART shares some features with Alzheimer disease (AD), such as progressive accumulation of neurofibrillary tangle pathology in the medial temporal lobe and other brain regions, it does not progress extensively to neocortical regions. Given this restricted pathoanatomical pattern and variable symptomatology, there is a need to reexamine and improve upon how PART is neuropathologically assessed and staged. We performed a retrospective autopsy study in a collection ($n=174$) of post-mortem PART brains and used logistic regression to determine the extent to which a set of clinical and neuropathological features predict cognitive impairment. We compared Braak staging, which focuses on hierarchical neuroanatomical progression of AD tau and A β pathology, with quantitative assessments of neurofibrillary burden using computer-derived positive pixel counts on digitized whole slide images of sections stained immunohistochemically with antibodies targeting abnormal hyperphosphorylated tau (p-tau) in the entorhinal region and hippocampus. We also assessed other factors affecting cognition, including aging-related tau astrogliopathy (ARTAG) and atrophy. We found no association between Braak stage and cognitive impairment when controlling for age ($p=0.76$). In contrast, p-tau burden was significantly correlated with cognitive impairment even when adjusting for age ($p=0.03$). The strongest correlate of cognitive impairment was cerebrovascular disease, a well-known risk factor ($p<0.0001$), but other features including ARTAG ($p=0.03$) and hippocampal atrophy ($p=0.04$) were also associated. In contrast, sex, *APOE*, psychiatric illness, education, argyrophilic grains, and incidental Lewy bodies were not. These findings support the hypothesis that comorbid pathologies contribute to cognitive impairment in subjects with PART. Quantitative approaches beyond Braak staging are critical for advancing our understanding of the extent to which age-related tauopathy changes impact cognitive function.

Keywords: PART, dementia, Aging, Braak, ARTAG

114 Introduction

115 It is widely recognized that abnormal hyperphosphorylated tau (p-tau) deposition is a ubiquitous feature
 116 of the aging human brain, observed in both cognitively normal subjects and in those with a range of
 117 clinical features, including cognitive, motor and psychiatric symptoms [37]. The causes of tauopathy are
 118 diverse, and include both genetic and environmental risk factors [48]. Autosomal dominant mutations in
 119 the tau gene (*MAPT*) cause frontotemporal lobar degeneration and common risk alleles, notably the
 120 *MAPT* 17q21.31 H1 haplotype, are associated with sporadic tauopathies including progressive
 121 supranuclear palsy (PSP), corticobasal degeneration (CBD), and argyrophilic grain disease (AGD) [12].
 122 Abnormal p-tau deposition is also seen following exposure to repetitive head trauma in contact sports
 123 and other contexts in the setting of chronic traumatic encephalopathy (CTE) [43]. Neurofibrillary tangles
 124 (NFT) are also a component of Alzheimer disease (AD), where they are associated amyloid-beta deposits
 125 [16].

126 Although it is generally understood that autopsy studies are critical for establishing definitive
 127 diagnoses, the neuropathology of the tauopathies is complex and overlapping. Further, non-impaired
 128 individuals often display significant amounts of p-tau accumulation, complicating our understanding of
 129 the contribution of such brain changes to symptomatology. Approaches to assessing tauopathy in post-
 130 mortem tissues continue to evolve. Neuropathologically, tauopathies can be differentiated by the
 131 neuroanatomical regionality of p-tau aggregates, cell type involvement (i.e., neurons versus glia),
 132 preferential isoform accumulation, and filament ultrastructure. Based upon these differentiating features,
 133 validated neuropathological diagnostic consensus criteria have been devised and, in some cases,
 134 undergone revision. Examples include revision of the AD diagnostic criteria, and consensus criteria for
 135 CTE [41, 46]. The term aging-related tau astrogliopathy (ARTAG), which was described in recent
 136 consensus criteria on various patterns of astrocytic p-tau observed in aging, has been especially helpful
 137 for differentiating age-related changes from CTE, both of which have perivascular p-tau deposits, but with
 138 differences in cell types involved [38, 42]. The introduction of criteria for primary age-related tauopathy

(PART) to describe individuals who develop AD-type neurofibrillary pathology with or without dementia in the absence of significant amyloid deposition helped to better define this entity and differentiated it from AD [17]. Understanding age-related tauopathy is of critical importance in the context of diagnosis and staging of all the tauopathies given its extremely high prevalence and importance as a co-morbidity in essentially all studies evaluating tauopathy.

There has been controversy surrounding the PART consensus criteria since their introduction [11, 19], and there have been a substantial number of recent clinicopathological studies focused on understanding this pathological presentation [4, 6, 7, 29, 33, 36, 51, 52, 60]. Given the close clinical and neuropathological similarities between PART and AD such that historically the two entities were classified together, accumulating evidence has highlighted differences. Clinically, the average age is higher for individuals who have PART than those with AD and patients with PART are more often female [35]. Patients with PART pathology are more often cognitively normal, but a subset have mild cognitive impairment or amnesic dementia, and this correlates with p-tau severity [17]. Among symptomatic individuals with a neuropathological diagnosis of PART, nearly half had been clinically diagnosed with AD compared with 86% of those with autopsy-confirmed AD, indicating that despite diagnostic uncertainty, clinicians recognize differences between the two [59]. One retrospective study identified other factors including depression, Braak stage, and history of stroke, as independent predictors of cognitive impairment [6]. Another found that those with PART had a sparing of semantic memory compared to those with AD, suggesting that there is a distinct difference in clinical presentation [8]. Longitudinal analyses found that subjects with PART have a significantly slower clinical decline after becoming symptomatic than those with AD across multiple neuropsychological domains [60].

One limitation of most published studies on PART is that they rely on retrospective analysis of previously collected datasets (e.g., the National Alzheimer's Coordinating Center database, NACC) with predefined neuropathological measures that may not fully capture all the clinically relevant features [45]. Further, findings might not be generalizable to other populations, and a lack of uniform analysis and

164 quantitation might lead to bias. Critically, the Braak staging system was specifically developed for
 165 assessment of tau pathology in the context of AD, and has not been rigorously tested in amyloid-negative
 166 subjects, so the extent to which it is valid for staging p-tau pathology in PART is unclear. Additionally, the
 167 Braak stage represents a hierarchical progression of the regional spread of neurofibrillary tangles, but
 168 does not directly measure the severity or burden of p-tau, but this has been incorporated into some
 169 operationalized frameworks [2]. Because the pathology in PART generally remains predominantly in the
 170 medial temporal lobe, this hierarchical pathoanatomical system may sub-optimally measure severity of
 171 the disease. There are numerous approaches to assessing lesion burden of p-tau and other pathologies
 172 [10, 28, 30, 31, 40, 41, 44, 63], including cell counting and stereology [3, 5, 13, 21, 27, 64]. While each
 173 of these approaches have intrinsic advantages, they are limited in that they are labor intensive and for
 174 this reason and others, these methods have not been widely adopted in neuropathology laboratories [20,
 175 62]. One approach that may have potential to better assess p-tau in PART is using computer-assisted
 176 quantitative morphometrics on digital whole slide images, which may be well suited for staging PART.

177 Here, we studied a cohort of autopsy-confirmed subjects with PART, enabling us to reexamine
 178 how tau pathology manifests in PART. We compared Braak staging with computer-assisted quantitative
 179 measures of p-tau burden, and used logistic regression to assess their contribution to cognitive
 180 impairment. Using this cohort, we were able to explore critical co-morbid pathologies (e.g.,
 181 cerebrovascular disease), and further assess neuropathological changes that are not available in existing
 182 publicly available datasets, including atrophy and ARTAG.

183 **Methods**

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185 Patient samples

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187 Formalin-fixed paraffin embedded (FFPE) tissue from the frontal cortex and hippocampus as well as
 188 fresh-frozen tissue from frontal cortex were derived from autopsy brains from a subset of individuals from
 189 a previously described collection [61]. Specifically, the cohort included cases from the Oregon Health
 190 Sciences University (Portland, OR, USA), Banner Sun Health Research Institute (Sun City, AZ, USA),
 191 Emory (Atlanta, GA, USA), Northwestern (Evanston, IL, USA), the University of Pennsylvania
 192 (Philadelphia, PA, USA), University of Pittsburgh (Pittsburgh, PA, USA), University of Texas
 193 Southwestern Medical Center (Dallas, TX, USA), and the Medical University of Vienna (Vienna, Austria).
 194 Clinical inclusion criteria included being cognitively normal or having a diagnosis of mild cognitive
 195 impairment (MCI) or dementia with a recorded clinical dementia rating (CDR), Mini-Mental State
 196 Examination (MMSE), or postmortem clinical chart review CDR score within two years of death [22, 47].
 197 CDR and MMSE scores were used to assign subjects into either cognitively normal or cognitively
 198 impaired groups. Individuals who had a CDR score of 0.5 or above or MMSE score below 26 were
 199 considered to be cognitively impaired while subjects with a CDR score of 0 or MMSE score 26 or above
 200 were considered cognitively normal [39]. If an individual had both MMSE score and CDR score, the most
 201 recent score was used, and if both scores were given on the same date, the CDR score was used.

202 Comprehensive neuropathological assessments were performed at the contributing institutions.
 203 Neuropathological criteria for PART included (1) cases that had a Braak stage of 0-IV and (2) Consortium
 204 to Establish a Registry for Alzheimer's Disease (CERAD) neuritic plaque severity score of 0 [10, 44].
 205 Neuropathological exclusion criteria consisted of other neurodegenerative diseases including AD, Lewy
 206 body disease, progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), chronic traumatic
 207 encephalopathy (CTE), Pick disease, Guam amyotrophic lateral-sclerosis-parkinsonism-dementia,
 208 subacute sclerosing panencephalitis, globular glial tauopathy. Data pertaining to Braak stage, CERAD,

209 Lewy body pathology (incidental), cerebrovascular disease, infarcts (vascular brain injury), microinfarcts,
210 and argyrophilic grains, were derived from neuropathologic studies performed at respective centers. The
211 presence of aging-related tau astrogliopathy (ARTAG) was determined on p-tau immunohistochemical
212 stains described below [38].

213

214 Atrophy score

215

216 Given that no widely accepted validated system for assessing hippocampal atrophy on human brain
217 sections exists, we devised a semiquantitative scoring system and applied it to low power images of
218 hematoxylin & eosin-stained sections counterstained with Luxol fast blue. We defined atrophy severity
219 as the magnitude of ventricular dilatation (hydrocephalus ex vacuo) relative to the size of the hippocampal
220 formation. If there was no apparent ventricular dilatation or atrophy, then a score of 0 was assigned. If
221 there was appreciable atrophy, but the dorsoventral height of the ventricle was less than the height of the
222 thickest section of CA1, then a score of 1 (mild) was assigned. If the magnitude of ventricular dilatation
223 exceeded the thickness of CA1, then a score of 2 (moderate) was given. If the total area of the ventricle
224 area was greater than the area of the hippocampus proper, a score of 3 (severe) was assigned. This
225 score was derived only in the subset of cases where the entire temporal horn of the lateral ventricle was
226 available included in the provided section ($n=24$).

227

228 Immunohistochemistry

229

230 Immunohistochemistry (IHC) and hematoxylin & eosin (H&E) stains were performed on FFPE sections
231 (5 μ m) that were prepared from blocks of hippocampus and frontal cortex for supplemental
232 neuropathological analyses (see below). Sections mounted on positively charged slides were dried
233 overnight at room temperature. IHC was performed on a Leica Bond III automated stainer, according to
234 the manufacturer's protocols (Leica Microsystems, Buffalo Grove, IL, USA). IHC was performed using

antibodies to hyper-phosphorylated tau (p-tau, AT8, 1:1000, Fisher Scientific, Waltham, MA) and beta-amyloid (A β , 6E10, 1:1000, Covance, Princeton, NJ, USA). A β stains were confirmed to be negative to ensure that there were no neuritic or diffuse plaques present (CERAD score of 0) for all cases. For each set of slides stained, a known severe AD case was included as a batch control.

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Computer-assisted morphometric analysis

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Whole slide images (WSI) were prepared from glass slides that were scanned using an Aperio CS2 (Leica Biosystems, Wetzlar Germany) digital slide scanner. Quantitative analysis of the tau burden was performed in selected regions in the hippocampi using the following methodology; WSI were neuroanatomically segmented using Aperio ImageScope software into the hippocampus proper (i.e., dentate, cornu ammonis, and subiculum) and the adjacent cortex that we termed the entorhinal region, which variably includes posterior portions of the parahippocampal gyrus with remnants of the (trans-)entorhinal region or lingual gyrus. Staining was measured in these areas separately and together using a modified version of the Aperio positive pixel count (Version 9) based on the intensities of the positive control sample in each batch to determine the area of immunoreactivity. Data were normalized using the number of positive pixel counts to the total area creating a 0-1 p-tau burden scale.

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Genetic analysis

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High-throughput isolation of DNA was performed using the MagMAX DNA Multi-Sample Ultra 2.0 Kit on KingFisher Flex robotic DNA isolation system (ThermoFisher, Waltham, MA). 20-40 mg of fresh frozen brain tissue were placed into a deep-well plate and treated with 480 μ l of Proteinase K mix (Proteinase K, Phosphate Buffered Saline [pH 7.4], Binding Enhancer) and incubated overnight at 65°C at 800 rpm on a shaking plate. Genomic DNA was isolated and purified using magnetic particles. DNA quality control was performed using a nanodrop spectrophotometer (concentration > 50ng/ μ l, 260/280 ratio 1.7-2.2).

Genotyping was performed using single nucleotide polymorphism (SNP) microarrays (Infinium Global Screening Array v2.4. or the Infinium OmniExpress-24, Illumina, San Diego CA). Raw genotype files were converted to PLINK-compatible files using GenomeStudio software (Illumina, San Diego CA). *MAPT* haplotype was determined using the rs8070723 H2 tagging SNP. *APOE* genotype was provided by the collaborating center. For analyses, the *APOE* status was collapsed into a binary variable of the presence or absence of *APOE* ε4.

Statistical analysis

All statistical tests were performed using the statistical software Statistical Package for the Social Sciences (SPSS) (IBM, Chicago, IL). Data was visualized using the ggplot2 package in project R or Excel (Microsoft, Redmond, Washington). Binary measurements (yes/no) were created for pathological, clinical, demographic, and genetic variables. Specifically, variables were extracted from the pathological diagnosis and binary measurements (yes/no) were created for the following variables: argyrophilic grains, Lewy body pathology (incidental), cerebrovascular disease, and infarcts (vascular brain injury). Additionally, the same process was done for clinical variables: history of psychiatric illness and education (for this study, defined as at least some college).

Descriptive statistics were used to identify differences between the cognitively normal and cognitively impaired PART groups for clinical, pathological, and genetic variables. Differences were detected using χ^2 tests or exact χ^2 if any cell size included < 5 participants. A t-test was performed to determine if age differed significantly between normal and cognitively groups. Next, an unadjusted binary logistic regression was performed to determine what genetic, clinical, and pathological variables were associated with being cognitively impaired within our PART cohort. Lastly, a multivariable model was created to determine what extent Braak NFT stage and the computer-assisted morphometrics were able to predict cognitive impairment in PART when adjusting for age. Statistical significance was determined if $\alpha < 0.05$. Not all data was available on the subjects.

Results

One hundred seventy-four neuropathologically confirmed amyloid-negative subjects were included in this study (Table 1, Figure 1). The overall mean age was 83.2 with a range of 52.9-105.1 years. Of these, 124 subjects (mean age 81.0, range = 52.9-102.4) had no cognitive impairment and 50 (mean age 88.3, range = 69.8-105.1) had some degree of cognitive impairment, with either mild cognitive impairment (MCI) or dementia. The majority of subjects who were cognitively impaired were 80+ years of age (Figure 2). The Braak NFT stage ranged from 0 to IV with the majority of cognitively impaired subjects having a Braak NFT score of II to IV. A higher percentage of females had cognitive impairment (62.0%) compared to those who were cognitively normal (49.2%).

We observed several differences among subjects with cognitive impairment compared to those who were cognitively normal. First, cognitively impaired PART subjects were more likely to be older (age of testing 81.0 vs. 88.3, $p < 0.0001$), have cerebrovascular disease (42.0% vs. 4.8%, $p < 0.0001$) and have hippocampal age-related tau astroglipathy (ARTAG; 38.3% vs. 21.6%, $p < 0.05$) compared to cognitively normal subjects (Table 1). However, education, history of psychiatric illness, argyrophilic grains, incidental Lewy body pathology, infarcts, presence of an *APOE* $\epsilon 2$ allele, presence of *APOE* $\epsilon 4$ allele, and *MAPT* haplotype status did not significantly affect cognitive status ($p > 0.05$ for all conditions).

In our main unadjusted analysis, we assessed the extent to which a series of clinical, neuropathological, and genetic variables predicted cognitive impairment in our PART cohort (Table 2). We found that age and cerebrovascular disease were the strongest predictors of cognitive impairment ($p < 0.0001$ for both cases). ARTAG and hippocampal atrophy were also significant predictors, but to a lesser extent ($p < 0.05$ for both cases). There were more reported men and subjects with a history of psychiatric illness, argyrophilic grains, incidental Lewy body pathology, infarcts, and microinfarcts in the cognitively impaired PART group, however none of these predictors was significantly different ($p > 0.05$ for all conditions). *APOE* $\epsilon 4$ (at least 1 $\epsilon 4$ allele) was reported more in the cognitively normal PART group but did not reach significance. Braak NFT stage significantly predicted cognitive impairment ($p < 0.05$).

313 Additionally, the computer-assisted morphometrics in the entorhinal region, hippocampus proper, and
 314 the combined region were significantly associated with cognitive impairment ($p = 0.0001$, Figure 3A-C,
 315 Table 3). Lastly, when the Braak NFT stage was correlated with computer-assisted morphometrics in the
 316 combined region ($p < 0.001$), there was a high degree of variability between the Braak NFT stage and
 317 the computer-assisted combined region morphometrics (Figure 3D).

318 Finally, using a multivariable model, we assessed whether any measurements for p-tau predicted
 319 cognitive impairment when controlling for age. In this adjusted analysis, we found that computer-assisted
 320 morphometrics used to capture p-tau burden in the hippocampus proper and combined region were
 321 significantly associated with cognitive impairment in PART ($p < 0.05$ for both cases). However, the
 322 computer-assisted morphometrics in the entorhinal region were not associated with cognitive impairment
 323 yet there was a trend toward statistical significance ($p = 0.068$). The Braak NFT stage was not able to
 324 predict cognitive impairment when controlling for age ($p = 0.73$, Table 3, Figure 4).

325 Discussion

326 Since the neuropathological criteria for PART were proposed, the terminology has been widely adopted,
 327 but controversy persists, especially around its relationship to Alzheimer disease (AD). Delineating the
 328 histological/cellular features that are associated with cognitive impairment in PART is critical for
 329 advancing our understanding of the pathology and determining the extent to which it overlaps with AD.
 330 The fact that subjects with PART, as with AD neuropathologic change, can range in their cognitive status
 331 from normal to demented, raises the question as to whether cognitive reserve/resilience plays a role or
 332 alternatively whether we are not adequately capturing the relevant features, such as common
 333 comorbidities or other factors. This study, by using a large autopsy cohort with multivariate analyses,
 334 directly addresses these critical questions. The goal was to leverage our collection of post-mortem PART
 335 brains to characterize the clinical, pathological, and genetic features that are associated with cognitive
 336 impairment in PART. Additionally, we sought to compare Braak stage with pathology burden measures
 337 derived from p-tau immunohistochemistry that quantifies severity independently of neuroanatomical
 338 vulnerability. To overcome intra-center variability in tau pathology measures, we reassessed each case
 339 histologically to maximize accuracy.

340 We found that all of our PART definite cases had p-tau restricted mainly to the MTL (Braak NFT
 341 stage <IV), which is consistent with and supports other previous studies investigating PART [4, 17, 34].
 342 Cases ranged in cognitive impairment with the majority of subjects being cognitively normal, and
 343 consistent with prior data, the PART subjects tended to be older than individuals with AD [17, 59]. The
 344 results of our study confirm those of previous autopsy studies showing that cerebrovascular disease
 345 predicts cognitive impairment in PART [6, 49]. Interestingly, we did not see a strong correlation between
 346 cognitive impairment and microinfarcts, while others have shown a correlation with cognition in the oldest
 347 old [14]. We did however, find novel, unreported associations of increased age, hippocampal atrophy,
 348 and ARTAG with cognitive impairment in our PART definite cohort. Similar to what has been reported
 349 by those utilizing the NACC database, our results verify those with a higher Braak NFT stage are
 350 associated with more rapid cognitive decline [33].

While these associations have yet to be reported in PART, there are numerous studies showing that age, atrophy, and ARTAG may be associated with cognitive impairment [9, 23, 32, 50, 53]. Surprisingly, we did not see increased odds of the Braak NFT stage being associated with cognitive impairment when controlling for age as has been reported in other studies [6]. However, we did find that using computer-assisted morphometrics to assess p-tau burden in the entorhinal region, hippocampus, and combined region was able to significantly predict cognitive impairment, similar to other studies [1, 13]. While Braak NFT staging is the most widely employed approach for assessing p-tau, it is limited in that it primarily focuses on regionality and not disease burden [25]. Other studies have employed both manual and computer assisted quantitative approaches that may capture aspects of pathological features with more power [24, 26, 56]. However, a majority of these approaches focuses on AD which may not be relevant in the context of PART, where p-tau pathology does not progress in the same hierarchical manner proposed by Braak in AD [10, 16]. Hence this study highlights several new methodologies to assess p-tau burden, which our results suggest to be a more accurate predictor of clinical symptomology in those with PART.

In addition to assessing p-tau burden, we also examined the effect of *APOE* status in PART as a predictor for cognitive impairment. *APOE* ϵ 4 has been strongly suggested as an important predictor of cognitive decline in AD while *APOE* ϵ 2 has been shown to be protective [15, 18, 54, 58]. However, many of these studies have been performed in AD cohorts, and in aging cohorts there has been evidence suggesting the ϵ 4 allele is not a risk factor for cognitive impairment [57]. Our data agree with that reported by Small *et al.* as we did not see an association with *APOE* ϵ 4 and cognitive impairment, which might be explained by the fact that we studied a pathologically confirmed amyloid-negative cohort. Recent work has suggested that *APOE* may exacerbate tau pathology independently of amyloid deposition [55]. Here, we failed to detect an association of cognitive impairment in PART with the *MAPT* H1 haplotype; future larger studies with more statistical power are required to delineate the genetic architecture of PART.

This study had notable limitations. There was a relatively small number of subjects in the cognitively impaired PART group ($n=50$), which may weaken our power to predict cognitive impairment.

377 Additionally, because a majority of our subjects were not from longitudinally studied prospective cohorts,
378 we were unable to obtain certain lifestyle variables, such as actual years of education and concussion
379 history, which could potentially significantly affect our model. However, given that diagnosing PART pre-
380 mortem is currently challenging, it would be impractical to create such a prospective cohort. We would
381 also like to highlight the association we observed with ARTAG and cognitive status might be only due to
382 collinearity between p-tau severity and ARTAG, with p-tau probably the driving pathology and the ARTAG
383 association being significant because of its potential dependence on p-tau. Lastly, our study was limited
384 to pathology of the medial temporal lobe and frontal cortex. A more exhaustive study would have
385 incorporated a greater number of brain regions to more extensively address other potential tau-related
386 pathologies.

387 In summary, our findings are consistent with the hypothesis that PART is an amyloid-independent
388 tauopathy, primarily affecting the medial temporal lobe, which can present with cognitive impairment.
389 Several demographic and neuropathological variables including age, ARTAG, cerebrovascular disease,
390 hippocampal atrophy, Braak NFT stage, and p-tau computer assessments were significantly associated
391 with cognitive impairment in our PART cohort. The Braak NFT stage was not a significant predictor of
392 cognitive impairment when controlling for age, while the computer-assistant morphometrics were. These
393 data strongly suggest that neuroanatomical staging used in AD may not be as relevant to PART given
394 the pathology minimally spreads beyond the medial temporal lobe. Novel techniques to measure p-tau
395 burden can further our understanding of PART pathology and associated clinical and genetic features.

396

Table 1. Patient data

	Overall	Cognitive Status		p
		Normal	Impaired*	
Demographics				
Average age at testing (range)	83.2 (52.9-105.1)	81.0 (52.9-102.4)	88.3 (69.8-105.1)	<0.0001
Total (Male / Female)	174 (82 / 92)	124 (63 / 61)	50 (19 / 31)	0.126***
Age at last visit (%)				
<60	7 (4.0)	7 (5.6)	0 (0.0)	
60-69	15 (8.6)	14 (11.3)	1 (1.7)	
70-79	33 (19.0)	30 (24.2)	3 (5.2)	
80-89	76 (43.7)	45 (36.3)	31 (53.4)	
90+	51 (29.3)	28 (22.6)	23 (39.7)	
Education, at least some college (%)	32 (18.4)	15 (78.9)	17 (77.3)	0.89
History of psychiatric illness (%)	45 (25.9)	29 (31.9)	17 (45.9)	0.13
Neuropathological data				
Argyrophilic grains	32 (18.4)	12 (9.7)	10 (20.0)	0.06
Lewy body pathology (incidental)	16 (9.2)	11 (8.9)	5 (10.0)	0.82
Cerebrovascular disease**	27 (15.5)	6 (4.8)	21 (42.0)	<0.0001
Infarcts (vascular brain injury)	37 (21.3)	24 (19.4)	13 (26.0)	0.33
Hippocampus ARTAG positive (%)	43 (24.7)	25 (21.6)	18 (38.3)	0.03
Genetic Data				
Presence of ≥1 APOE ε4 allele	22 (12.6)	16 (12.9)	6 (11.3)	0.77
Presence of ≥1 APOE ε2 allele	46 (26.4)	27 (21.8)	19 (35.8)	0.06
Presence of ≥1 MAPT H2	59 (33.9)	42 (36.2)	17 (36.2)	1

* Mild cognitive impairment or dementia, ** excluding cerebral amyloid angiopathy, ***Male sex, significant values in bold (Chi squared test)

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Table 2. Unadjusted odds of being cognitively impaired

	OR	95% CI	p value
<i>Characteristic</i>			
Age, at testing	1.08	1.04-1.13	<0.0001
Education, y	0.87	0.67-1.12	0.28
Sex	1.69	0.86-3.30	0.13
APOE (at least 1 ε4 allele)	0.988	0.36-2.70	0.98
History of psychiatric diagnosis	1.82	0.83-3.98	0.14
Aging-related tau astroglipathy (ARTAG)	2.26	1.08-4.72	0.03
Argyrophilic grains	2.33	0.94-5.82	0.07
Lewy body pathology (incidental)	1.14	0.38-3.47	0.82
Cerebrovascular disease*	14.24	5.27-38.48	<0.0001
Infarcts (vascular brain injury)	1.46	0.68-3.17	0.33
Microinfarcts	1.05	0.43-2.59	0.91
Hippocampal atrophy	5.32	1.04-27.09	0.04
Braak NFT stage	1.37	1.03-1.83	0.03
<i>Computer-assisted p-tau (AT8) burden (positive pixel counts)</i>			
Entorhinal region	1.90	1.31-2.75	0.001
Hippocampus proper	2.17	1.48-3.20	<0.0001
Entorhinal region & Hippocampus proper	2.12	1.44-3.11	<0.0001

* Excluding cerebral amyloid angiopathy, significant values in bold (logistic regression)

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Table 3. Odds of being cognitively impaired at death, adjusted

	OR	95% CI	<i>p</i> value
Braak NFT stage	1.01	0.72-1.41	0.98
P-tau burden (computer-assisted AT8 IHC positive pixels)			
Entorhinal region	1.46	0.97-2.20	0.07
Hippocampus	1.66	1.07-2.57	0.02
Entorhinal region & hippocampus	1.62	1.06-2.49	0.03
Significant values in bold (logistic regression)			

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Figure 1

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406 **Figure 1. Comparison of amyloid and tau pathology in primary age-related tauopathy**
 407 **(PART) versus Alzheimer disease (AD). (A) Immunohistochemical staining using antisera**
 408 **to hyperphosphorylated tau in an AD brain shows marked hyperphosphorylated tau (p-tau)-**
 409 **containing neurofibrillary tangles (NFT) in the hippocampus which extends past the collateral**
 410 **sulcus into the parahippocampal gyrus and other neocortical regions. (B, C) Subjects with mild**
 411 **to severe PART have elevated p-tau levels in the hippocampus predominantly restricted to the**
 412 **medial temporal lobe. (D, E, F) Subjects with AD neuropathologic change have abundant Aβ-**
 413 **containing plaques in neocortical structures, whereas those with PART have sparse or none.**
 414 **These neuropathologic changes in AD and PART are seen in association with varying degree**
 415 **of cognitive impairment ranging from cognitively normal to demented.**

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Figure 2

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422 **Figure 2. Distribution of age, Braak neurofibrillary tangle (NFT) stage and cognitive**

423 **status.** (A) The number of normal and cognitively impaired subjects across the age spectrum.

424 (B) The number of cognitively normal and impaired subjects by Braak stage. (C) The number

425 of subjects across the aging spectrum by Braak stage.

426

Figure 3

427

428 **Figure 3. Computer-assisted morphometrics to assess pathological tau burden. (A, B)**
429 Quantitative assessment of hyperphosphorylated tau (p-tau) burden was performed on whole
430 slide images of the hippocampus stained for p-tau (AT8) using immunohistochemistry. Positive
431 pixel counts were determined in two regions (hippocampus proper and entorhinal region).
432 Results were normalized to the total area assessed. A third summary score of the total p-tau
433 burden of the medial temporal lobe was calculated by summing positive pixels in both. (C) High
434 power image shows high intensity in red, medium intensity in yellow and negative staining in
435 blue. (D) Parallel plot showing the relationship between Braak stage and the computer

436 morphometric quantification of p-tau using the normalized medial temporal lobe (hippocampus
437 and entorhinal region). Scale bar = 150 μm .

438

Figure 4

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440 **Figure 4. Pathological tau burden in normal and cognitively impaired subjects across the**
441 **aging spectrum. (A-C)** Generalized linear models of age versus tau burden show significant
442 differences between cognitively normal and cognitively impaired subjects in the hippocampus
443 proper ($p = 0.047$), and combined entorhinal region and hippocampus regions ($p < 0.048$), but
444 not in the entorhinal region alone ($p = 0.07$). **(D)** Generalized linear model of age vs Braak NFT
445 staging did not show significant differences between cognitively normal and cognitively impaired
446 subjects ($p = 0.73$).

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