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RESEARCH ARTICLE

Significance of a positive tau PET scan with a negative amyloid PET scan

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Abstract

INTRODUCTION: The implications of positive tau positron emission tomography (T) with negative beta amyloid positron emission tomography (A) are not well understood. We investigated cognitive performance in participants who were T+ but A-.

METHODS: We evaluated 98 participants from the Mayo Clinic who were T+ and A-. Participants were matched 2:1 to A- and T- cognitively unimpaired (CU) controls. Cognitive test scores were compared between different groups.

RESULTS: The A-T+ group demonstrated lower performance than the A-T- group on the Mini-Mental Status Exam (MMSE) ($p < 0.001$), Wechsler Memory Scale-Revised Logical Memory I ($p < 0.001$) and Logical Memory II ($p < 0.001$), Auditory Verbal Learning Test (AVLT) delayed recall ($p = 0.004$), category fluency (animals $p = 0.005$; vegetables $p = 0.021$), Trail Making Test A and B ($p < 0.001$), and others. There were no significant differences in demographic features or apolipoprotein E (APOE) e4 genotype between CU A-T+ and CI A-T+.

DISCUSSION: A-T+ participants show an association with lower cognitive performance.

KEYWORDS
Alzheimer's disease, amyloid PET, cognition, FTP-PET, tau, tauopathies

1 | INTRODUCTION

The National Institute on Aging—Alzheimer's Association (NIA-AA) introduced a research framework that is based on a biomarker-based definition of Alzheimer's disease (AD).[1] Rather than focusing on clinical symptoms when making a diagnosis of AD, this framework provides a biologically based definition of AD. The biomarker-based framework, known as AT(N), recognizes three general groups of biomarkers: beta-amyloid (Aβ) deposition, pathologic tau (T), and neurodegeneration (N).[1] According to the AT(N) framework, individuals with abnormal Aβ deposition are classified as being on the AD continuum, without consideration of clinical symptoms.[1] Individuals who have normal Aβ levels but demonstrate abnormal tau, with or without neurodegeneration, however, are classified as being outside of the Alzheimer's continuum. There is very little known about individuals who reside outside of the Alzheimer's continuum with normal Aβ levels and abnormal tau with or without neurodegeneration. Therefore, it is crucial to develop an understanding of the disease course of individuals with divergent underlying pathologic processes.

There are a limited number of reports of individuals who have negative Aβ positron emission tomography(A) and positive tau positron emission tomography (PET) (T). Individuals who demonstrate this biomarker profile have been described as belonging to one of two categories: suspected non-Alzheimer's pathophysiology (SNAP) or primary age-related tauopathy (PART).[2–4] SNAP characterizes individuals with abnormal neurodegeneration and tau uptake in the absence of Aβ.[2,5,6] The SNAP classification also indicates that other neuropathologic processes leading to neurodegeneration may be at work that are not likely to include AD.[7] PART is a neuropathological diagnosis delineated as having mild/moderate tau deposition in the absence of Aβ pathology.[8–12] In PART, neurofibrillary tau tangles (NFT) affect brain regions that are also affected in the early/moderate stages of typical AD such as the medial temporal lobe. However, individuals with PART typically display milder cognitive impairment compared to those with AD.[9,10,13] Further, PART includes individuals both with and without cognitive impairment.[2,13,14] Understanding the pathologic processes underlying these less common biomarker profiles is critical in order to determine the prognosis and potential treatments for such individuals.

To address this knowledge gap, the current study aimed to determine the effects of abnormal accumulation of neuronal tau on cognitive function in participants displaying normal amounts of Aβ based on PET imaging. We hypothesized that an increase in tau protein alone would be associated with a decline in cognition.

RESEARCH IN CONTEXT

1. **Systematic review**: An improved understanding of the relationship between beta-amyloid (Aβ) and neuronal tau and how they affect cognitive function is needed. Presently, there is relatively little known about individuals with normal Aβ levels and abnormal tau. We aimed to determine the effects of abnormal tau positron emission tomography (PET) (T) on cognitive function in participants with no Aβ detected on PET imaging (A-).
2. **Interpretation**: We examined differences in cognitive functioning between participants who A-T- and A-T+. The A-T+ group had lower though still normal cognitive performance.
3. **Future directions**: Future studies should consider the patterns of both A and T in longitudinal neuroimaging to clarify the biomarker trajectories of these individuals.

2 | METHODS

2.1 | Participants

Participants were selected from the Mayo Clinic Study of Aging (MCSA) and the Mayo Clinic Alzheimer's Disease Research Center (ADRC). The MCSA is a randomized, population-based, cohort study that examines normal cognitive aging in addition to mild cognitive impairment (MCI) and dementia.[15] The Mayo Clinic ADRC is a clinic-based referral study that focuses on investigating and understanding normal brain aging, MCI, and AD and related dementias. In our cohort, MCSA participants represent about 2/3 of the A-T+ sample and ADRC represent about 1/3.

At the time of study design there were a total of 1192 participants who underwent flortaucipir (FTP) PET and Pittsburg compound-B (PiB) PET imaging. Ninety-eight of these individuals (8.2%) were determined to be positive for tau protein and negative for Aβ using a standardized uptake value ratio (SUVr). The cutoff for amyloid positivity was ≥1.48 and the cutoff for tau positivity was ≥1.29 as described by previous investigations.[16–18] Participant images were also visually analyzed by expert radiologists. On visual inspection, two (2%) A-T+ participants appeared to be A+. Since SUVr was the criterion used for entry into the study, we included these individuals in the analyses.

2.2 | Clinical diagnoses

Participants were diagnosed with MCI if they reported problems with memory, had objective memory impairment for their age, had relatively preserved general cognitive functioning and functional abilities, and did not have dementia.[19] A diagnosis of frontotemporal lobar degeneration (FTLD) was made if participants demonstrated a progressive decline in behavior or language associated with frontal and anterior temporal lobe degeneration.[20] Participants were diagnosed with AD if they had Aβ plaques and pathologic tau as defined by in vivo biomarkers according to the criteria provided in the NIA-AA research framework.[1] Participants were diagnosed with probable or possible dementia with Lewy bodies (DLB) according to the fourth consensus

report of the DLB Consortium.[21] Similarly, participants were diagnosed with possible DLB if they demonstrated progressive cognitive decline and exhibited only one of the core clinical features or had one or more of the indicative biomarkers present,[21] in the absence of core clinical features. In keeping with Gorno–Tempini's classification of primary progressive aphasia (PPA), a diagnosis of PPA was rendered if a participant's most prominent clinical feature was language difficulty and aphasia was the most pronounced deficit at symptom onset and in initial phases of disease course.[22] All participants were diagnosed at a consensus meeting including a neurologist, neuropsychometrist, and a nurse or study coordinator.

2.3 | Clinical and neuropsychological examinations

2.3.1 | ADRC

The Clinical Dementia Rating Scale (CDR) sum of boxes was utilized to measure dementia severity.[23] The Mini-Mental State Examination (MMSE) was used to assess general cognitive function.[24] We evaluated verbal learning and memory with the Auditory Verbal Learning Test (AVLT)[25] and Wechsler Memory Scale-Revised Logical Memory, language with category verbal fluency (Strauss et al., 2006), and processing speed/mental flexibility with the Trail Making Test (TMT) Parts A and B.[26] The Wechsler Adult Intelligence Scale-Revised (WAIS-R) Block Design subtest examined visuospatial processing. We used the Movement Disorders Society-sponsored revision of the Unified Parkinson's Disease Rating Scale part III (UPDRS III) to assess parkinsonism.[27]

2.3.2 | MCSA

We used the delayed recall trials from the AVLT and the WMS-R Logical Memory and Visual Reproduction subtests to assess memory. Category fluency[28] assessed language. The WAIS-R Block Design subtest examined visuospatial processing. The Trail Making Test Part B[28,29] assessed mental flexibility.

2.4 | Neuroimaging

T1-weighted MRI scans were acquired using 3T scanners manufactured by GE and Siemens using Magnetization Prepared Rapid Acquisition Gradient–Recalled Echo (MPRAGE) sequences. Tau-PET images were acquired after participants were injected with 370 MBq (range 333–407 MBq) of F18-flortaucipir, and amyloid PET with 628 MBq (range 385–723 MBq) of 11C-PiB. A 20-min dynamic PET scan with four 5-min frames was acquired 80–100 min after AV14151 injection and 40–60 min after PiB injection. Dynamic PET images were generated (256 matrix, 300 mm field of view, 1.17 mm × 1.17 mm × 3.27 mm voxel size) using an iterative reconstruction algorithm. Standard corrections for attenuation, scatter, randoms, and decay were applied as well as a 5 mm Gaussian post filter. The images from the four dynamic frames were summed to create a static image.

2.5 | Image analysis

The static PET images were preprocessed with our in-house image processing pipeline.[20] Briefly, the PET scans were rigidly co-registered to the corresponding MRI and subsequently warped to Mayo Clinic Adult Lifespan Template (MCALT) space. SUVr was calculated by dividing the median uptake in the cerebellar crus gray matter. This region avoids any off target white matter signal in the cerebellum with the amyloid tracer and any off-target tau that sometimes occurs in the central cerebellum. The T meta region of interest (ROI) was used and consists of the entorhinal, amygdala, parahippocampal, fusiform, inferior temporal, and middle temporal. The A meta-ROI was also used and consisted of the prefrontal, orbitofrontal, parietal, temporal, anterior and posterior cingulate, and precuneus. Cortical ROI's were defined by an in-house version of the automated anatomic labeling atlas. The meta-ROI SUVr was calculated as an average of the median uptake across regions of meta-ROIs.

T and A were assessed quantitatively and visually to determine A and T positivity/negativity. Participants were selected for tau positivity using a cutoff value of ≥1.29 and amyloid negativity using a SUVr cutpoint value of <1.48. Individual scans were also examined visually for uptake. For visual analysis, the images were reviewed on a computer workstation showing three standard orthogonal views, and cortical areas with uptake greater than background cortical uptake were considered positive.

2.6 | Statistical analysis

For statistical analyses, we analyzed variables in a combined group of MCSA and ADRC participants (MCSA/ADRC group) and we also analyzed variables in a group of MCSA only participants (MCSA only group). The rationale for doing so was to investigate the effects of abnormal tau in the general population depicted by the MCSA-only group since the majority of these participants are cognitively normal. Likewise, because the ADRC participants are generally more impaired, we are able to examine different phenotypes between ADRC participants and MCSA participants. A 2:1 matching on age and sex for A-T- participants from the MCSA was selected as a comparison group. Participant characteristics were summarized with the mean (standard deviation) for continuous variables and count (percentage) for the categorical variables. Conditional logistic regression models that take into account the matching were used to compare A-T- and A-T+ groups. The unimpaired A-T+ compared to the impaired A-T+ were analyzed with a *t*-test for continuous variables and a chi-square for categorical variables with the reported mean (standard deviation) and count (percentages), respectively, summarizing their characteristics. Tau SUVr values were analyzed with a natural log-transformation due to skewness. Statistical significance was set at $p < 0.05$ (two-tailed) in all analyses.

TABLE 1 Characteristics of matched CU A-T- versus A-T+ (mean (SD) for continuous variables and count (%) for categorical variables).

	MCSA and ADRC with respective matches			MCSA only with respective matches		
	A-T- $n = 196$	A-T+ $n = 98$	p-Value	A-T- $n = 128$	A-T+ $n = 64$	p-Value[a]
Age, yr	72.3 (11.2)	72.3 (11.3)	0.73	74.9 (10.1)	74.9 (10.1)	0.86
Males, no. (%)	126 (64%)	63 (64%)	1.00	80 (62%)	40 (62%)	1.00
Education, yrs	15.3 (2.6)	14.9 (2.4)	0.14	15.3 (2.4)	14.6 (2.1)	0.068
MMSE	28.7 (1.1)	27.1 (3.2)	<0.001	28.7 (1.0)	28.1 (2.0)	0.022
CDR SOB	0.0 (0.1)	1.3 (2.4)	<0.001	0.0 (0.2)	0.2 (0.7)	0.10
UPDRS score	0.4 (1.4)	1.6 (3.9)	0.003	0.5 (1.4)	0.6 (1.7)	0.77
APOE e4 carriers, no. (%)	46 (25%)	12 (13%)	0.016	32 (27%)	6 (10%)	0.010
PiB SUVr	1.37 (0.07)	1.38 (0.07)	0.36	1.38 (0.07)	1.38 (0.06)	0.38
Tau SUVr	1.15 (0.07)	1.36 (0.09)		1.15 (0.07)	1.33 (0.04)	
APOE e4 carriers, no. (%)	46 (25%)	12 (13%)	0.016	32 (27%)	6 (10%)	0.010
Diagnosis						
Cognitively unimpaired	196 (100%)	56 (57.1%)		128 (100%)	53 (82.8%)	
MCI		16 (16.3%)			9 (14.1%)	
Uncertain		5 (5.1%)			1 (1.6%)	
FTD		6 (6.1%)				
DLB		6 (6.1%)				
AD		1 (1.0%)				
Progressive fluent aphasia		2 (2.0%)				
Progressive associative agnosia		1 (1.0%)				
Logopenic progressive aphasia		2 (2.0%)				
Paraneoplastic		1 (1.0%)				
Dementia-hard to classify		1 (1.0%)			1 (1.6%)	
Prior mental deficit-static		1 (1.0%)				

[a]p-values based on a conditional logistic model accounting for matching.

3 | RESULTS

3.1 | Participant characteristics

The characteristics of study participants are displayed in Table 1. There were no significant differences in demographic features or A SUVr between the combined MCSA/ADRC group or the MCSA only group. There was, however, a difference in APOE e4 genotype between groups. In the MCSA/ADRC group, 25% of A-T- and 13% of A-T+ participants were APOE e4 carriers ($p = 0.016$), and in the MCSA only group, 27% of A-T- participants and 10% of A-T+ participants were APOE e4 carriers ($p = 0.010$). In the MCSA/ADRC group, the A-T- participants performed better on the MMSE ($p < 0.001$), CDR Sum of Boxes (CDR SOB) ($p < 0.001$), and UPDRS ($p = 0.003$) compared to the A-T+ group. In the MCSA only group, A-T- participants had a statistically slightly higher score on the MMSE than the A-T+ group ($p = 0.022$), while there were no significant differences between groups on the CDR SOB and UPDRS.

Table 2 shows the neuropsychological variables for the combined MCSA/ADRC group and the matched MCSA only group. For the combined ADRC/MCSA sample, the A-T+ group had lower performance than the A-T- group on all neuropsychological measures. In particular, the A-T+ group had poorer performance on Logical Memory I and II and the Trail Making Test. In the MCSA-only group, the A-T+ group had lower scores on Logical Memory II ($p = 0.022$), AVLT delayed recall ($p = 0.04$), and Block Design ($p = 0.035$).

3.2 | A-T+ participant characteristics

The characteristics of cognitively unimpaired (CU) and cognitively impaired (CI) A-T+ participants are displayed in Table 3. In the A-T+ group, 56 (57.1%) participants were CU and 42 (42.9%) were CI. There were no significant differences in demographic features or APOE e4 genotype between CU A-T+ and CI A-T+. However, although not statistically different, CI A-T+ tended to be younger than CU A-T+. Interestingly, CI A-T+ participants also had significantly lower PiB SUVr ($p = 0.020$) and significantly higher tau SUVr compared to CU A-T+ ($p = 0.003$).

TABLE 2 Neuropsychological test scores (raw) for CU A-T- versus A-T+ (mean (SD) for continuous variables and count (%) for categorical variables).

	MCSA and ADRC with respective matches			MCSA only with respective matches		
	A-T- $n = 196$	A-T+ $n = 98$	*p*-Value	A-T- $n = 128$	A-T+ $n = 64$	*p*-Value[b]
Logical Memory I	26.0 (7.5)	18.4 (10.3)	<0.001	25.5 (7.5)	23.8 (8.0)	0.16
Logical Memory II	22.9 (8.3)	14.9 (9.9)	<0.001	22.3 (8.4)	19.0 (9.3)	0.022
AVLT Delayed Recall	8.7 (3.4)	7.1 (4.0)	0.004	8.5 (3.4)	7.3 (3.9)	0.040
Category Fluency (Animals)	20.1 (4.9)	17.9 (7.1)	0.005	19.9 (4.8)	19.9 (6.0)	0.94
Category Fluency (Vegetables)	12.4 (3.3)	11.2 (5.1)	0.021	12.2 (3.3)	12.7 (4.8)	0.41
[a]Trail Making Test A	35.3 (11.7)	46.4 (31.2)	<0.001	36.7 (12.4)	38.0 (18.5)	0.40
[a]Trail Making Test B	81.0 (40.5)	108.0 (71.9)	<0.001	84.7 (39.7)	96.0 (64.4)	0.12
Block Design	29.2 (9.3)	24.1 (10.9)	0.002	28.7 (9.4)	25.6 (10.2)	0.035

[a]Higher scores denote worse performance.
[b]*p*-values based on a conditional logistic model accounting for matching.

TABLE 3 Characteristics of cognitively unimpaired A-T+ versus impaired A-T+ (mean (SD) for continuous variables and count (%) for categorical variables).

	CU $n = 56$	Impaired $n = 42$	*p*-Value[a]
Age, yr	74.1 (10.0)	69.9 (12.5)	0.067
Males, no. (%)	35 (62%)	28 (67%)	0.67
Education, yr	15.0 (2.1)	14.7 (2.6)	0.49
APOE, no. (%)	6 (11%)	6 (16%)	0.49
MMSE	28.7 (1.0)	24.6 (3.8)	<0.001
CDR SOB	0.1 (0.2)	3.0 (2.9)	<0.001
UPDRS score	0.2 (0.6)	3.7 (5.4)	<0.001
PiB SUVr	1.39 (0.05)	1.36 (0.08)	0.020
Tau SUVr	1.33 (0.04)	1.39 (0.13)	0.003

[a]*p*-values based on T-tests for continuous variables and chi-squared for categorical variables.

3.3 | FTP-PET elevation by ROIs

Figure 1 displays a bar graph depicting the visual assessment of tau positivity in each ROI for the A-T+ group. The x-axis is the percentage of visually assessed abnormality across each ROI. The left temporal inferior, left temporal mid, right temporal inferior, right temporal mid, in addition to the angular gyrus, orbitofrontal cortex, fusiform gyrus, and occipital lobe were the most consistently positive in this sample.

3.4 | Visual analysis

Only two PiB scans appeared to be visually positive. FTP scans showed positive uptake in 60 participants. Of those 60 scans, 58 were A- and 2 were A+.

3.5 | FTP-PET elevation participant examples

Figure 2 displays examples of visually identified patterns of FTP binding in participants from the A-T+ group. While there was some off-target binding, the regions showing off-target binding do not encroach on other positive regions. Some A-T+ participants displayed a pattern with bilateral tau signal only in the medial temporal lobes (possibly PART). For example, case #7 displayed a mild bilateral medial temporal FTP binding pattern that could reflect PART. Some A-T+ participants demonstrated mild, and in others widespread, cortical uptake that included bilateral temporal regions but also more widespread cortical regions like parietal and frontal lobes (cases #1 and #3). Case #1 showed mild, widespread cortical temporal uptake, and Case #3 showed temporal and frontal cortical binding on quantitative and visual assessment. This could reflect TDP-43 pathology and is consistent with these participants' clinical diagnoses of FTD. Further, some participants in the A-T+ group had variable regions of AD-level tau signal (cases #2, #4, #5, and #6). Case #2 had an AD-like level of binding with intense asymmetric left dominant temporal parietal binding. Case #4 showed a high level of bilateral, frontal prominent cortical signal most similar to early-onset AD. Case #5 had an atypical binding pattern with widespread focal areas of signal with some off-target binding in the meninges. Case #6 had AD-like level of binding with intense asymmetric left dominant temporal and parietal binding consistent with the participant's diagnosis of lvPPA. Case #8 had mild diffuse cortical tau uptake.

3.6 | Cognition and clinical diagnoses

Figure 3 shows cognitive profile comparisons, and clinical diagnoses among the A-T- group and the A-T+ group in both the combined MCSA/ADRC group and the matched MCSA only group. In the combined MCSA/ADRC group and matched MCSA only group, the cognitive performance of the A-T+ group was poorer compared to the

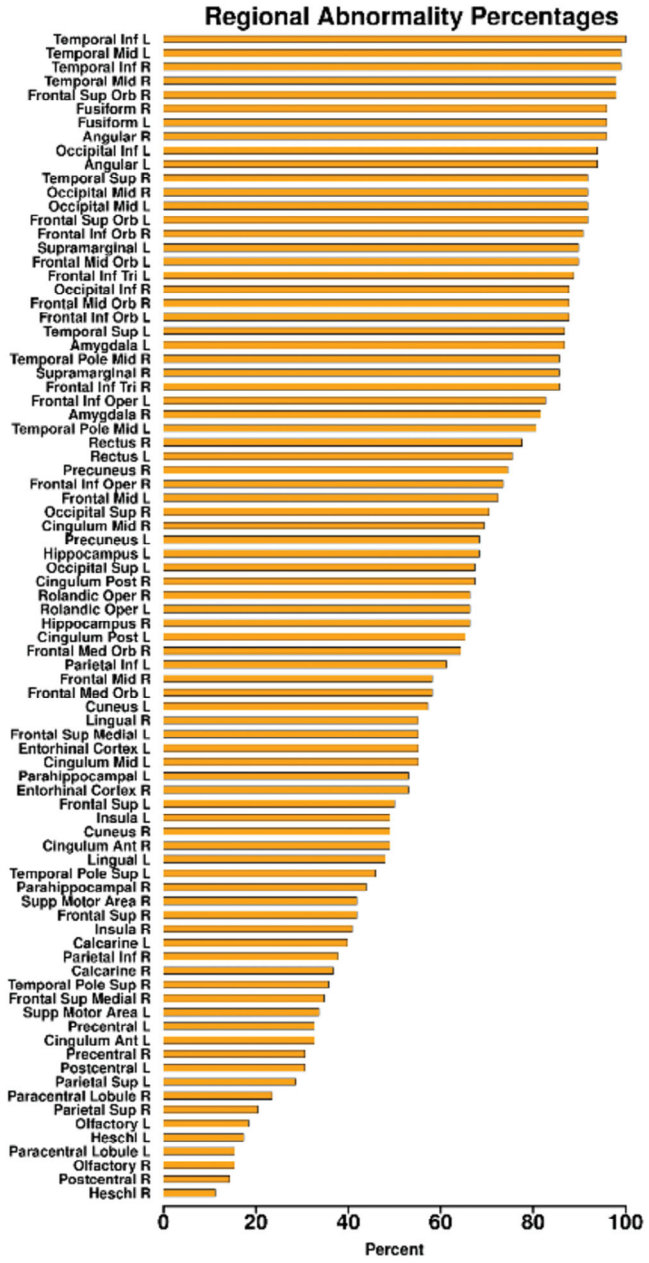

FIGURE 1 The topography of tau distribution. The x-axis is the percentage of each brain region visually assessed as being positive.

A-T- group on measures of Logical Memory I (p = <0.001) and Logical Memory II (p = < 0.001). In the MCSA only group, the A-T+ group displayed poorer performance on Logical Memory II (p = 0.02). The clinical diagnoses included AD, MCI, DLB, FTD, and uncertain/other. The MCI diagnoses consisted of 11 amnestic with four being single domain and seven having multi-domains. There were four non-amnestics with three having single domain and one with multi-domain. The FTD diagnoses included progressive fluent aphasia/semantic dementia, progressive associative agnosia, and logopenic progressive aphasia. The other/uncertain diagnoses consisted of hard to classify dementia (primarily vascular), prior mental deficiency static, and paraneoplastic. Notably, all of those with clinically relevant findings leading to a diagnosis were A-T+, and these participants mostly presented with lower scores, most apparent in Logical Memory. The most common diagnosis in the A-T+ group was MCI. Figures S1 and S2 display cognitive profile comparisons and clinical diagnoses among the A-T- group and the A-T+ group.

3.7 | Genetic mutations

Of the 34 participants with genetic data available, the majority were on the DLB spectrum (n = 12), 2 were familial prion, 3 MAPT, 4 FTD, and 8 suspected TDP-43. There were also a few anomalies with brain tumor resection and traumatic brain injury (TBI).

4 | DISCUSSION

In this study, we identified 98 participants who demonstrated positive tau in the absence of Aβ out of a total of 1192 participants completing both amyloid and tau scans. Our resulting A-T+ group demonstrated normal levels of Aβ on amyloid PET that did not differ from the A-T- group. Although there were no significant baseline differences in demographic features between groups, aside from APOE status, we found differences in cognitive functioning on neuropsychological measures.

Within the combined MCSA/ADRC sample, the A-T+ group performed lower on measures of immediate/delayed verbal memory, semantic fluency, processing speed, mental flexibility, visuospatial function, general cognitive function, and parkinsonism. Regarding worse scores in parkinsonism, measured by the UPDRS, we believe this could be due to a mix of pathologies within the A-T+ group; specifically, Lewy Body pathology. In the MCSA only cohort, this was limited to delayed verbal memory and visuospatial function. Furthermore, within the A-T+ group, we observed that 42.9% of the A-T+ participants were CI and 57.1% were CU. Although there were no significant differences between CU A-T+ and CI A-T+ in demographic features or APOE e4 genotype, CI A-T+ participants had a lower PiB SUVr and a higher tau SUVr compared to CU A-T+. While we do not have definite reason for this finding, we speculate that subthreshold amyloid may play an uncertain role in tau aggregation. This finding suggests that tau aggregation influences cognitive function in the context of low or minimum amyloid. We also found that the A-T+ group had a lower proportion of APOE e4 carriers compared to the A-T- group, which is consistent with the PART literature.[8–12] Further, the lower cognitive performance in the A-T+ group is consistent with previous reports of cognitive impairment and dementia within PART participants.[9] However, there are also reports of PART participants demonstrating no cognitive impairment or mild cognitive impairment, which is also consistent with our investigation given not all of the participants in the A-T+ group had significant cognitive impairment.[9,30,31]

Regarding lower cognitive functioning on neuropsychological measures within the A-T+ group, previous investigations have reported similar findings in A-T+ participants. An investigation in 2020 by

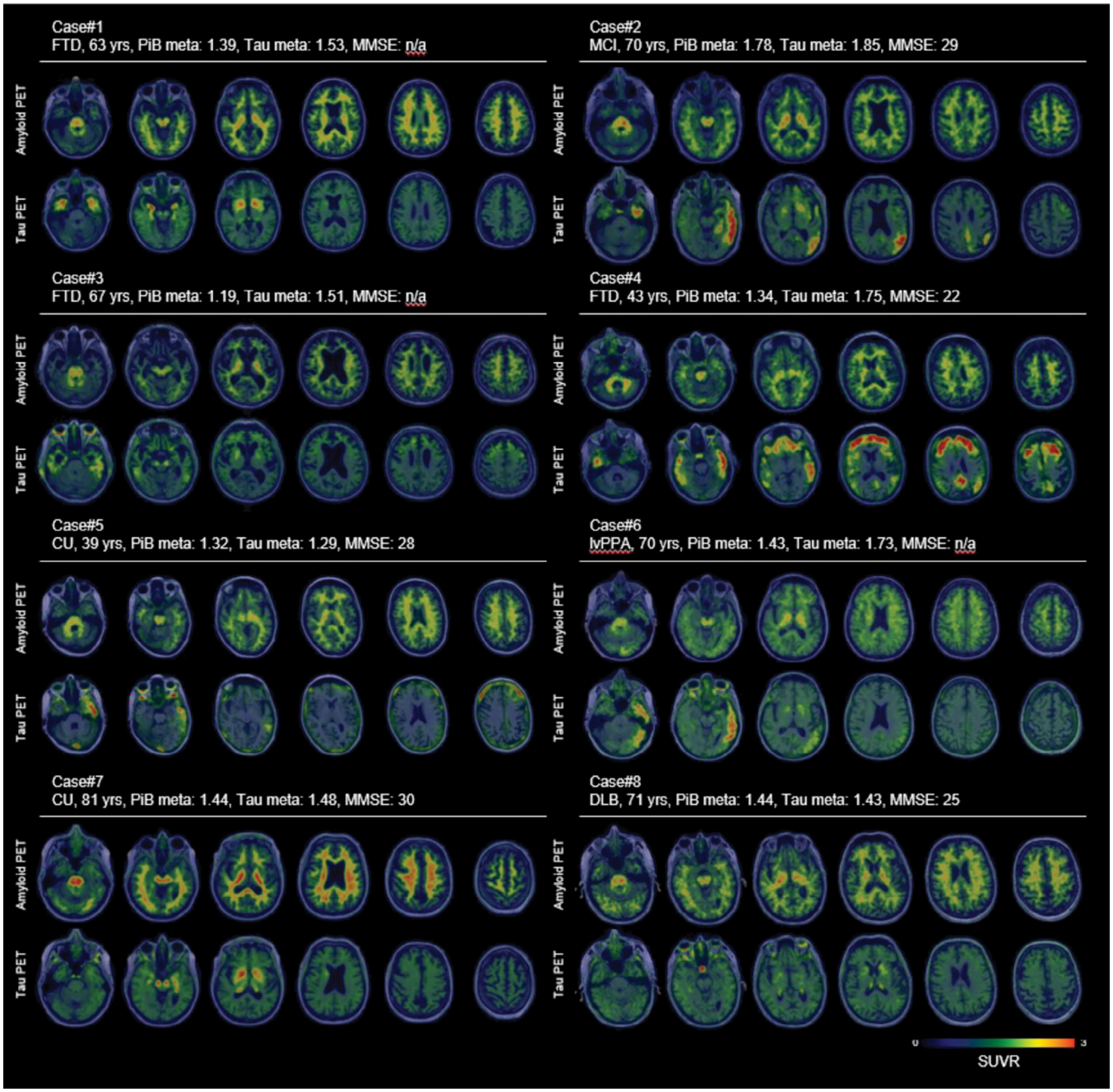

FIGURE 2 Heterogeneous patterns of Flortaucipir (FTP) binding in the A-T+ group (SUVr values are shown). Each image consists of an FTP positron emissions tomography (PET) scan that was co-registered with the corresponding magnetic resonance image (MRI) (grayscale). Clinical presentations of each participant are listed. Key: Pittsburgh compound-B (PiB), Mini-Mental Status Exam (MMSE), frontotemporal dementia (FTD), logopenic primary progressive aphasia (lvPPA), mild cognitive impairment (MCI), dementia with Lewy bodies (DLB), cognitively unimpaired (CU), positron emission tomography (PET), standardized uptake value ratio (SUVr).

Weigand et al., found that relative to A-T- participants and A+T- participants, A-T+ participants performed more poorly across memory, language, and executive function domains.[32] An additional study conducted by Weigand et al. in 2022 demonstrated that compared to A-T- participants, A-T+ participants demonstrated lower scores on AVLT delayed recall and naming in addition to part B.[33] Further, an investigation by Josephs et al. looking at clinical features in definite PART participants showed that tau was associated with poorer cognitive performance without the presence of amyloid.[10] Correspondingly, findings from a study conducted by Landau & Mormino further indicate that an increase in medial temporal lobe tau, without amyloid, is associated with cognitive decline.[34] The association between tau and lower cognitive performance has been inconsistent with some prior tau PET investigations.[35] However, since participants in this study had a more limited tau distribution than the present study it is difficult to compare these results. Taken together, these findings suggest

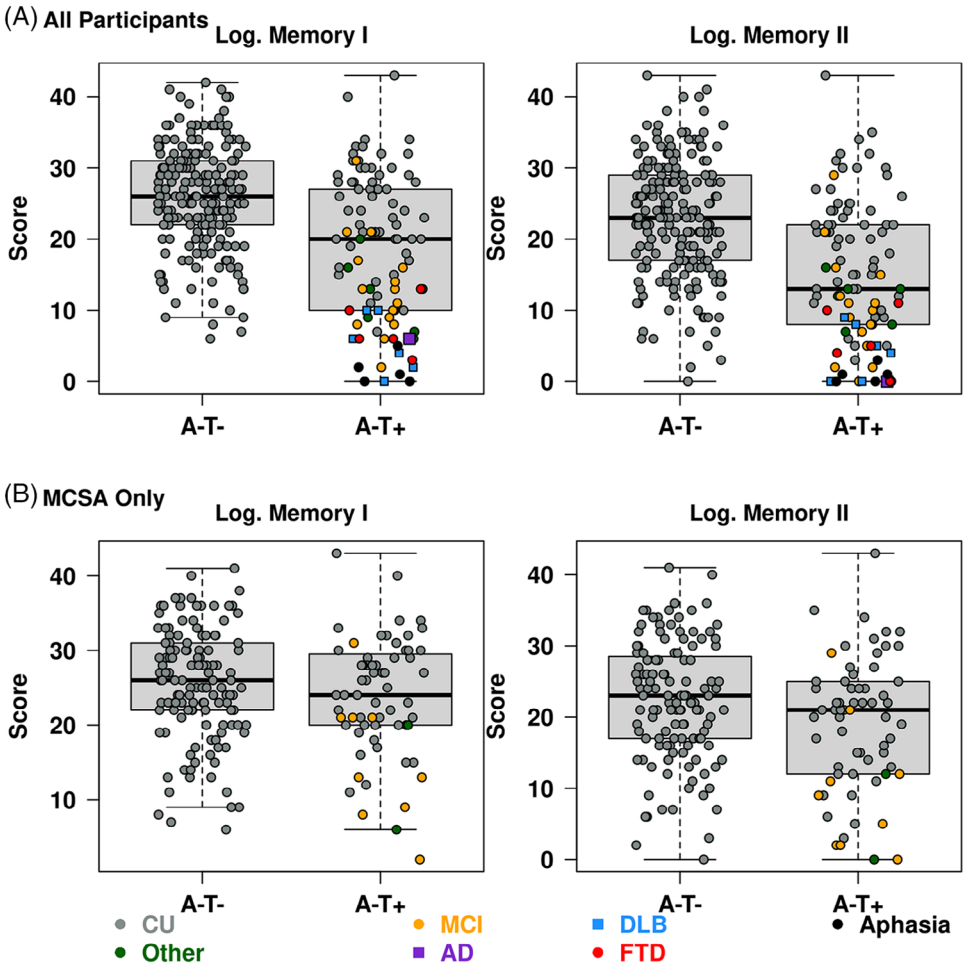

FIGURE 3 Cognitive profile comparisons and clinical diagnoses among the A-T- group and the A-T+ group. The x-axis is the group designation and the y-axis shows the raw scores of each cognitive measure. Key: frontotemporal dementia (FTD), mild cognitive impairment (MCI), Alzheimer's disease (AD), dementia with Lewy bodies (DLB).

that the A-T+, is likely associated with poorer cognitive performance and may be best described as a clinical syndrome, some of which can be described pathologically as PART. However, it is also important to note that additional pathologies such as vascular disease may be influencing cognitive function in the A-T+ group. Future correlations with vascular disease biomarkers and other biomarkers may improve our understanding of the nature of poorer cognitive performance in A-T+ groups.

Quantitative and visual review of the A-T+ tau PET scans showed that tau signal in the medial temporal lobes was the most common and could be a pattern suggestive of PART.[9,36] A previous investigation, conducted by Yoon et al., similarly demonstrated that 28.6% of their A-T+ participants displayed a pattern of bilateral medial temporal binding.[37] Individuals with this pattern may be more likely to demonstrate normal cognition than individuals with more advanced tau signal in this region. There were other tau binding patterns that may indicate more extensive temporal lobe involvement and/or distant tau involvement. The brain regions with the highest tau uptake in the A-T+ group were the medial, lateral, and inferior temporal regions in addition to the angular gyrus, orbitofrontal cortex, fusiform gyrus, and occipital lobe. Similarly, Yoon et al. found that the regions with the highest tau uptake in the A-T+ group were the amygdala, entorhinal, lateral orbitofrontal, inferior temporal, banks superior temporal, pars orbitalis, temporal pole, precuneus, pericalcarine, fusiform, pars triangularis, middle temporal, and insula.[37] These findings suggest tau signal in A-T+ can be seen in non-AD dementias, typical early AD, have PART-like uptake, or even show advanced tau AD neuropathological patterns in rare cases (Figure #2, Case #6). Considering A-T+ an early form of AD may suggest that tau signal is preceding amyloid deposition in the AD process in a few individuals or that PET is not identifying some participants with low threshold amyloid or is falsely negative because of technical issues. Further follow-up of these individuals will help to elucidate these possibilities.

Neuroimaging studies have suggested that the Aβ pathway in AD demonstrates a spatial temporal progression of Aβ accumulation that first occurs in cerebral regions where there are high metabolic bio-energetic activity rates (such as the association cortices) and later advances from neocortex to allocortex until it extends to the cerebellum.[38,39] Aβ accumulation by way of this pathway seems to occur antecedent to the spread of NFTs and neuronal and synaptic death.[38] There is also genetic evidence that provides support for the role of the Aβ pathway in AD.[38] Further, it has been shown that Aβ

and tau pathology have disparate temporal sequences. Aβ is already present in the neocortex decades before the manifestation of clinical AD symptoms, and the rate of Aβ accumulation is reduced at the clinical stage of AD.[39] Likewise, the brain areas that are affected by neurodegeneration in AD are not strongly correlated with the locations of Aβ deposition.[39] Tau pathology, on the other hand, has strong spatial and temporal correlations with neurodegeneration and cognitive impairment in AD.[39] Neuroimaging has demonstrated colocalization with typical NFT neuropathology of AD but also some discordant areas of FTP uptake.[18] The findings in this work suggest that some tau signal can be reflected by FTP and can be independent of amyloid but have a similar cortical distribution to that seen in AD. Three of the example participants show FTD syndromes, with one showing mild FTP signal (likely TDP off-target implications, #1) and 2 showing high FTP signal suggesting primary tauopathies (#'s 3 and 4). The elevated FTP signal could be due to primary tauopathies that could be amyloid independent.

This study has many strengths, including having a relatively large cohort of A-T+ participants well matched with an A-T- group. We were able to contrast the possible findings from a more selected MCSA/ADRC sample and purely population based MCSA cohort which allows readers to apply this data to the general cognitively normal public. Because utilizing a quantitative threshold for tau/amyloid positivity can lead to misidentification and false positives or negatives, possibly from off-target binding or region registration errors, we reduced classification errors by visually analyzing all patient images. In addition, all patient scans were visually reviewed by the same expert radiologists. Our investigation was limited in that we lacked confirmatory neuropathology for these participants; however, this would be a goal of future work. Further, the cohort was 98% White and non-Hispanic participants. There were 3 (1%) Black/African American, 2 (0.7%) Asian, 1 (0.34%) multi-racial, and 288 (98%) White participants. Thus, we acknowledged the predominantly White racial/ethnic composition of the sample is a limitation of this investigation, and results may not be applicable to individuals of other ethnicities.

5 | CONCLUSION

This investigation of A-T+ participants demonstrates that lower cognitive performance can occur in the absence of Aβ. Determining whether these participants truly reflect a PART diagnosis or other pathology will depend on future longitudinal neuroimaging and neuropathologic studies examining the presence of Aβ in these participants later in disease course.

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CONFLICT OF INTEREST STATEMENT

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CONSENT STATEMENT

This study was approved by the Mayo Clinic Institutional Review Board and all patients, or their proxies signed a written informed consent form before taking part in any research activities in accordance with the Declaration of Helsinki.

DATA AVAILABILITY STATEMENT

Anonymized data are available from the corresponding author upon request from any qualified investigator and suitable proposal for purposes of replicating procedures and results.

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REFERENCES

1. Jack CR, Bennett DA, Blennow K, et al. NIA-AA Research Framework: toward a biological definition of Alzheimer's disease. *Alzheimers Dement*. 2018;14(4):535-562.
2. Yoon B, Guo T, Provost K, et al. Abnormal tau in amyloid PET negative individuals. *Neurobiol Aging*. 2022;109:125-134.
3. Lowe VJ, Wiste HJ, Senjem ML, et al. Widespread brain tau and its association with ageing, Braak stage and Alzheimer's dementia. *Brain*. 2018;141(1):271-287.
4. Jack CR, Wiste HJ, Knopman DS, et al. Rates of β-amyloid accumulation are independent of hippocampal neurodegeneration. *Neurology*. 2014;82(18):1605-1612.
5. Jack CR, Knopman DS, Weigand SD, et al. An operational approach to National Institute on Aging-Alzheimer's Association criteria for preclinical Alzheimer disease. *Ann Neurol*. 2012;71(6):765-775.
6. Lowe VJ, Lundt ES, Albertson SM, et al. Neuroimaging correlates with neuropathologic schemes in neurodegenerative disease. *Alzheimers Dement*. 2019;15(7):927-939.
7. Jack CR, Bennett DA, Blennow K, et al. NIA-AA Research Framework: toward a biological definition of Alzheimer's disease. *Alzheimers Dement*. 2018;14(4):535-562.
8. Kim D, Kim H-S, Choi S-M, et al. Primary age-related tauopathy: an elderly brain pathology frequently encountered during autopsy. *J Pathol Transl Med*. 2019;53(3):159-163.
9. Bell WR, An Y, Kageyama Y, et al. Neuropathologic, genetic, and longitudinal cognitive profiles in primary age-related tauopathy (PART) and Alzheimer's disease. *Alzheimers Dement*. 2019;15(1):8-16.
10. Josephs KA, Murray ME, Tosakulwong N, et al. Tau aggregation influences cognition and hippocampal atrophy in the absence of beta-amyloid: a clinico-imaging-pathological study of primary age-related tauopathy (PART). *Acta Neuropathol*. 2017;133(5):705-715.
11. Crary JF, Trojanowski JQ, Schneider JA, et al. Primary age-related tauopathy (PART): a common pathology associated with human aging. *Acta Neuropathol*. 2014;128(6):755-766.
12. Zhang X, Sun B, Wang X, et al. Phosphorylated TDP-43 staging of primary age-related tauopathy. *Neurosci Bull*. 2019;35(2):183-192.
13. Besser LM, Crary JF, Mock C, Kukull WA. Comparison of symptomatic and asymptomatic persons with primary age-related tauopathy. *Neurology*. 2017;89(16):1707-1715.
14. Jack CR, Bennett DA, Blennow K, et al. A/T/N: an unbiased descriptive classification scheme for Alzheimer disease biomarkers. *Neurology*. 2016;87(5):539-547.
15. Roberts RO, Geda YE, Knopman DS, et al. The Mayo Clinic study of aging: design and sampling, participation, baseline measures and sample characteristics. *Neuroepidemiology*. 2008;30(1):58-69.
16. Jack CR, Wiste HJ, Weigand SD, et al. Defining imaging biomarker cut points for brain aging and Alzheimer's disease. *Alzheimers Dement*. 2017;13(3):205-216.
17. Jack CR, Therneau TM, Weigand SD, et al. Prevalence of biologically vs clinically defined Alzheimer spectrum entities using the National Institute on Aging-Alzheimer's Association Research Framework. *JAMA Neurol*. 2019;76(10):1174-1183.
18. Lowe VJ, Lundt ES, Albertson SM, et al. Tau-positron emission tomography correlates with neuropathology findings. *Alzheimers Dement*. 2020;16(3):561-571.
19. Petersen RC. Mild cognitive impairment as a diagnostic entity. *J Intern Med*. 2004;256(3):183-194.
20. Rabinovici GD, Miller BL. Frontotemporal lobar degeneration: epidemiology, pathophysiology, diagnosis and management. *CNS Drugs*. 2010;24(5):375-398.
21. Mckeith IG, Boeve BF, Dickson DW, et al. Diagnosis and management of dementia with Lewy bodies: fourth consensus report of the DLB Consortium. *Neurology*. 2017;89(1):88-100.
22. Gorno-Tempini ML, Hillis AE, Weintraub S, et al. Classification of primary progressive aphasia and its variants. *Neurology*. 2011;76(11):1006-1014.
23. Morris JC. The clinical dementia rating (CDR): current version and scoring rules. *Neurology*. 1993;43(11):2412-2414.
24. Folstein MF, Folstein SE, Mchugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12(3):189-198.
25. Rey A. *L'examen clinique en psychologie*. Presses Universitaires de France; 1964.
26. Reitan RM. Validity of the trail making test as an indicator of organic brain damage. *Percept Mot Skills*. 1958;8(3):271-276.
27. Goetz CG, Tilley BC, Shaftman SR, et al. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. *Mov Disord*. 2008;23(15):2129-2170.
28. Strauss E, Sherman EMS, Spreen O. *A Compendium of Neuropsychological Tests*. Oxford University Press; 2006.
29. Reitan R. Validity of the trail making test as an indicator of organic brain damage. *Percept Mot Skills*. 1958;8:271-276.
30. Nelson PT, Abner EL, Schmitt FA, et al. Brains with medial temporal lobe neurofibrillary tangles but no neuritic amyloid plaques are a diagnostic dilemma but may have pathogenetic aspects distinct from Alzheimer disease. *J Neuropathol Exp Neurol*. 2009;68(7):774-784.
31. Jefferson-George KS, Wolk DA, Lee EB, McMillan CT. Cognitive decline associated with pathological burden in primary age-related tauopathy. *Alzheimers Dement*. 2017;13(9):1048-1053.
32. Weigand AJ, Bangen KJ, Thomas KR, et al. Is tau in the absence of amyloid on the Alzheimer's continuum?: a study of discordant PET positivity. *Brain Commun*. 2020;2(1):fcz046.
33. Weigand AJ, Edwards L, Thomas KR, Bangen KJ, Bondi MW. Comprehensive characterization of elevated tau PET signal in the absence of amyloid-beta. *Brain Commun*. 2022;4(6):fcac272.
34. Landau SM, Mormino EC. Tau pathology without Abeta-A limited PART of clinical progression. *JAMA Neurol*. 2023:80(10):1025-1027.
35. Krishnadas N, Doré V, Groot C, et al. Mesial temporal tau in amyloid-beta-negative cognitively normal older persons. *Alzheimers Res Ther*. 2022;14(1):51.
36. Lowe VJ, Wiste HJ, Senjem ML, et al. Widespread brain tau and its association with ageing, Braak stage and Alzheimer's dementia. *Brain*. 2017;141(1):271-287.
37. Yoon B, Guo T, Provost K, et al. Abnormal tau in amyloid PET negative individuals. *Neurobiol Aging*. 2022;109:125-134.
38. Hampel H, Hardy J, Blennow K, et al. The amyloid-β pathway in Alzheimer's disease. *Mol Psychiatry*. 2021;26(10):5481-5503.
39. Van Der Kant R, Goldstein LSB, Ossenkoppele R. Amyloid-β-independent regulators of tau pathology in Alzheimer disease. *Nat Rev Neurosci*. 2020;21(1):21-35.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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