Received: 8 August 2023 | Revised: 14 November 2023 | Accepted: 20 November 2023

DOI: 10.1002/alz.13609

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

RESEARCH ARTICLE

Individuals with Alzheimer's disease and low tau burden: Characteristics and implications

Susan M. Landau[1] | JiaQie Lee[1] | Alice Murphy[1] | Tyler J. Ward[1] | Theresa M. Harrison[1] | Suzanne L. Baker[2] | Charles DeCarli[3] | Danielle Harvey[3] | Duygu Tosun[4] | Michael W. Weiner[4,5,6] | Robert A. Koeppe[7] | William J. Jagust[1,2] | for the Alzheimer's Disease Neuroimaging Initiative

[1]Helen Wills Neuroscience Institute, University of California, Berkeley, California, USA

[2]Molecular Biophysics and Integrated Bioimaging, Lawrence Berkeley National Laboratory, Berkeley, California, USA

[3]School of Medicine, University of California, Davis, Sacramento, California, USA

[4]Department of Radiology and Biomedical Imaging, University of California, San Francisco, California, USA

[5]Department of Veterans Affairs Medical Center, Northern California Institute for Research and Education (NCIRE), Center for Imaging of Neurodegenerative Diseases, San Francisco, California, USA

[6]Department of Medicine, Department of Psychiatry and Behavioral Sciences, Department of Neurology, University of California, San Francisco, California, USA

[7]Department of Radiology, University of Michigan, Ann Arbor, Michigan, USA

Correspondence
Susan M. Landau, Helen Wills Neuroscience Institute, University of California, 18 Barker Hall MC #3190, UC Berkeley, Berkeley, CA 94720-3190, USA.
Email: slandau@berkeley.edu

Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in the analysis or the writing of this report.
A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wpcontent/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

Funding information
the Alzheimer's Disease Neuroimaging Initiative (ADNI); National Institutes of Health, Grant/Award Number: U01 AG024904; the National Institute on Aging; the National Institute of Biomedical Imaging and Bioengineering; Dementias (CARD)

Abstract

INTRODUCTION: Abnormal amyloid-beta (Aβ) and tau deposition define Alzheimer's Disease (AD), but non-elevated tau is relatively frequent in patients on the AD pathway.

METHODS: We examined characteristics and regional patterns of 397 Aβ+ unimpaired and impaired individuals with low tau (A+T−) in relation to their higher tau counterparts (A+T+).

RESULTS: Seventy-one percent of Aβ+ unimpaired and 42% of impaired Aβ+ individuals were categorized as A+T− based on global tau. In impaired individuals only, A+T− status was associated with older age, male sex, and greater cardiovascular risk. α-synuclein was linked to poorer cognition, particularly when tau was low. Tau burden was most frequently elevated in a common set of temporal regions regardless of T+/T− status.

DISCUSSION: Low tau is relatively common in patients on the AD pathway and is linked to comorbidities that contribute to impairment. These findings have implications for the selection of individuals for Aβ- and tau-modifying therapies.

KEYWORDS
Alzheimer's disease, Aβ PET, florbetaben, florbetapir, flortaucipir, tau PET

1 | INTRODUCTION

Amyloid-β (Aβ) plaques and pathological tau aggregates detected in vivo in cognitively impaired individuals are the characteristics of biomarker-defined Alzheimer's disease,[1] but Aβ and tau accumulation and cognitive decline are dynamic processes that progress over the course of disease. Abnormal Aβ accumulation occurs at least a decade before the onset of cognitive impairment, whereas medial temporal and neocortical tau accumulation occur later, are closely related to impairment and, together with Aβ, predict future decline.[2,3] There is also considerable variability in Aβ and tau burden throughout disease progression.

Based on the Alzheimer's Disease National Institute on Aging–Alzheimer's Association (NIA-AA) Research Framework and forthcoming Revised Criteria for Diagnosis and Staging of AD, "Core 1" biomarkers that reflect early Aβ abnormality such as Aβ positron emission tomography (PET)+ status (A+) define whether individuals are on the AD pathway, and "Core 2" biomarkers such as tau PET (T+/−) reflect a later stage of disease progression and are correlated with symptoms.[1,4] In Aβ+ individuals who are cognitively normal, tau burden that is within the normal range in medial and lateral temporal regions likely reflects an early stage of disease and is consistent with their lack of impairment. Among impaired Aβ+ individuals, however, tau within the normal range (A+T− status) represents an atypical course of disease that is nonetheless relatively common[5–9] but poorly understood. A+T− individuals are characterized as experiencing "Alzheimer's pathologic change," which is considered an early stage of disease, as opposed to "Alzheimer's disease" (A+T+) which requires evidence of elevated tau[1] and is presumed to reflect more progressed disease. However, in A+T− cognitively impaired patients, factors that account for impairment despite normal tau burden are unclear due to our limited ability to measure the full spectrum of age-related neuropathologies in vivo, but autopsy studies have shown that TDP-43, vascular pathology, and α-synuclein frequently accompany Aβ and account for a substantial proportion of cognitive symptoms in clinically-diagnosed AD.[10–13]

Understanding the characteristics of A+T− and A+T+ individuals is important because A+/− and T+/− criteria are increasingly used for participant selection in trials of Aβ- and tau-modifying therapies. Impaired patients with tau in the normal range were excluded from participation in recent Aβ-modifying[14] and tau-modifying therapies,[15] raising questions about the prevalence of such individuals and how their treatment response would compare to their higher tau counterparts who were enrolled in these trials.

The goal of this study was to determine which demographic, health, and biomarker characteristics are associated with low tau in individuals on the AD pathway. We examined characteristics of A+T− unimpaired and impaired participants from the Alzheimer's Disease Neuroimaging Initiative (ADNI) in relation to their A+T+ counterparts across a variety of demographic, health/cardiovascular risk, biomarker, and cognitive measurements, using average tau burden across a global cortical region to define T+/−. Our use of global tau for our primary T+/− definition is consistent with recent clinical trial approaches[14] and was intended to capture heterogeneous patterns of tau accumulation[16] as well as to avoid regional bias related to T+/− group membership for our subsequent region-wise "maximum tau" group analysis. We also carried out regression models to determine the joint contributions of tau and comorbid disease to continuous measures of cognitive performance in order to determine which factors may account for impairment when tau is low. To quantify comorbidities, we used cardiovascular risk as a representative measure of vascular disease, and α-synuclein (measured in cerebrospinal fluid [CSF] with the seed amplification assay) as a representative marker of age-related neuropathology other than Aβ and tau. We predicted that comorbidities would be more predictive of cognitive performance in the absence of abnormal tau for impaired patients only. Finally, we identified regions in which tau is consistently highest in A+T− and A+T+ groups in order to determine whether the regional distribution of tau accumulation is consistent even when tau is low.

RESEARCH IN CONTEXT

1. **Systematic review**: We used PubMed to identify publications examining variability in tau burden among unimpaired and impaired individuals on the Alzheimer's disease (AD) pathway based on abnormal Aβ burden. The prevalence and clinical characteristics of individuals with abnormal Aβ burden (Aβ+) but subthreshold tau are poorly understood.
2. **Interpretation**: Our findings indicate that male sex, older age, and elevated cardiovascular risk are more likely in impaired Aβ+, low tau individuals, and further, that the presence of α-synuclein has the strongest effect on cognition when tau is low.
3. **Future directions**: This manuscript describes the frequency of subthreshold tau in patients on the AD pathway, and identifies characteristics and comorbidities common to such patients that influence cognitive performance. These findings may inform the selection of individuals likely to benefit from anti-Aβ and tau therapies.

2 | METHODS

2.1 | Study design and participants

Participants in this study included individuals enrolled in ADNI with at least one Aβ PET and one tau PET scan and a corresponding magnetic resonance imaging (MRI) scan available as of July 2022 ($N = 890$), focusing on Aβ PET+ individuals for the majority of analyses ($N = 397$; 168 unimpaired, 229 impaired). ADNI participant characteristics have been previously described; all were between ages 55 and 90 years at baseline, had completed at least 6 years of education, were fluent in Spanish or English, and were free of any other significant neurologic

diseases. Individuals diagnosed with AD and mild cognitive impairment (MCI) met standard diagnostic criteria and all cognitively normal participants (with or without a subjective cognitive complaint) had Clinical Dementia Rating scores of 0.[17] The ADNI protocol was approved by local Institutional Review Boards (IRBs) and written informed consent was obtained from all participants.

2.2 | Aβ PET imaging and analysis

Aβ PET images consisted of 4 × 5 minute frames acquired at 50 to 70 minutes ([18F] florbetapir [FBP]) or 90 to 110 minutes ([18F] florbetaben [FBB]) post-injection. Frames were realigned, averaged, resliced to a common voxel size (1.5 mm^3), smoothed to a common resolution of 8 mm^3 full width at half maximum (FWHM), and coregistered to T1 MR images (MPRAGE) that were acquired concurrently with the baseline PET images (mean time interval: 0.1 ± 0.5 years). These structural scans were used to define cortical summary (frontal, cingulate, parietal, temporal) and reference regions (whole cerebellum. A total of 64% of the sample had available longitudinal Aβ PET data (see Table 1), and a composite reference region used for longitudinal analyses[18] in native space for each individual using Freesurfer v7.1 and converted to centiloids (CL) as described previously.[19] Aβ positivity thresholds (FBP: 1.11/20 CL, FBB: 1.08/18 CL) were defined based on an upper limit of Aβ standard uptake value ratios (SUVrs) in independent samples of young controls processed using the same pipeline for each tracer.[19]

2.3 | Hippocampal volumes

Hippocampal volume was defined on T1-weighted images acquired concurrently with the baseline Aβ PET scan (mean time interval 0.16 ± 0.47 years) using Freesurfer v7.1 and adjusted for head size by regressing out the relationship between hippocampal volume and intracranial volume (ICV) using the ICV mean of 283 Aβ− healthy controls and the slope of the hippocampal volume and total ICV relationship[20]: $HV_{adj} = .00329(ICV) - 1432.55$.

2.4 | Fluorodeoxyglucose PET

Glucose metabolism was calculated in template space for each individual using study-independent, previously-validated AD-specific regions of interest (ROIs; right and left inferior temporal and lateral parietal regions, and a bilateral posterior cingulate cortex region) that were averaged together and divided by the mean of a pons and cerebellar vermis reference region.[21]

2.5 | Tau PET scans

[^{18}F]Flortaucipir (FTP)-PET images consisted of 6 × 5 minute frames acquired at 75 to 105 minutes post-injection which were realigned, averaged, resliced to a common voxel size (1.5 mm^3), and smoothed to a common resolution of 8 mm^3 FWHM (http://adni-info.org). FTP scans were coregistered to a contemporaneous MRI scan, and FTP SUVRs in the following Freesurfer-defined regions were calculated relative to inferior cerebellar gray matter uptake[22]: entorhinal cortex, temporal metaROI (entorhinal, amygdala, parahippocampal, fusiform, inferior temporal, and middle temporal),[23] and a global tau region made up of medial and lateral temporal and extratemporal neocortical regions (see Supplementary Materials). Hippocampus was excluded due to off-target signal contamination.[22] We defined the following tau PET positivity thresholds in each tau PET ROI based on the 90th percentile of 287 ADNI Aβ− cognitively unimpaired individuals: entorhinal cortex, 1.23; temporal metaROI, 1.26; global region, 1.16. Longitudinal tau PET data was available for approximately 50% of the sample (impaired: 91/168, 54%; impaired, 113/229, 49%; see Table 1).

2.6 | CSF and plasma ptau181

CSF ptau181 data (available for 46% of the sample; see Table 1) was analyzed at the University of Pennsylvania using the Roche Elecsys immunoassay and protocol.[24] Plasma ptau181 (available for 39% of the sample) was analyzed using SIMOA and an in-house assay at the University of Gothenburg.[25]

2.7 | Plasma neurofilament light

Plasma neurofilament light (NfL) data (also available for 46% of the sample; see Table 1) was analyzed by the Blennow Lab with SIMOA using a home brew kit (Quanterix Corporation) as previously described.[26]

2.8 | Cognitive assessments

We used the Mini-Mental State Examination (MMSE)[27] and the Preclinical Alzheimer Cognitive Composite (PACC) scores[28] measured at the time of the baseline tau scan (time interval: 0.09 ± 0.14 years). About 75% of the sample (298/397 individuals) had longitudinal cognitive data acquired at approximately annual intervals (average follow-up 2.4 ± 1.2 years; also see Table 1), using test scores acquired no earlier than 6 months prior to the baseline tau PET scan.

2.9 | Comorbidities

2.9.1 | Cardiovascular and cerebrovascular risk

We calculated 10-year risk of a cardiovascular event using the non-laboratory test-based Framingham Risk Score (FRS), a model-derived

TABLE 1 Demographic, health risk, biomarker, and cognitive characteristics associated with high/low tau status among ADNI Aβ+ unimpaired and impaired groups.

		Unimpaired			Impaired		
		A+T−	A+T+	pval	A+T−	A+T+	pval
	N	119	49		96	133	
Participant characteristics	Subjective memory complaint (%)	9%	31%	**0.003**	–	–	–
	EMCI/LMCI/AD (%)	–	–	–	14/58/28	9/46/45	**0.03**
	Age (yrs)	74.2 ± 7.9	76.2 ± 6.1	ns	77.7 ± 8.5	74.4 ± 7.6	**0.004**
	Sex (%F)	59%	63%	ns	33%	53%	**0.004**
	Racial group (%URG)	11.8%	10.2%	ns	4.2%	12.8%	**0.026**
	Education (years)	16.7 ± 2.4	16.6 ± 2.2	ns	16.3 ± 2.6	15.5 ± 2.4	**0.01**
	APOE4 carriers (%)	49%	58%	ns	62%	69%	ns
Comorbid disease and pathology	# Overall health conditions	11.6 ± 7.2	15.1 ± 9.1	**0.01**	12.5 ± 8.0	12.3 ± 9.0	ns
	# Cardiovascular conditions	1.2 ± 1.1	1.5 ± 1.2	ns	2.0 ± 1.8	1.4 ± 1.5	**0.01**
	Framingham Risk Score	25 ± 15	29 ± 17	ns	32 ± 17	25 ± 15	**<0.001**
	Hypertension (%)	48%	51%	ns	62%	40%	**0.002**
	Hyperlipidemia (%)	55%	63%	ns	57%	47%	0.12
	Diabetes (%)	9%	12%	ns	14%	11%	ns
	Modified Hachinski > 0 (%)	51%	50%	ns	59%	46%	**0.04**
	White matter hyperintensities (adj)	1.32 ± .94	1.58 ± .97	0.12	1.80 ± 1.05	1.54 ± 0.92	**0.05**
	α-synuclein+	14/84 (17%)	13/42 (31%)	0.055	18/69 (26%)	31/107 (29%)	ns
Amyloid	Amyloid PET (CL)	50 ± 30	65 ± 34	**0.003**	70 ± 32	89 ± 34	**<0.001**
	Annual CL change	3.6 ± 3.1	5.0 ± 4.7	0.090	4.3 ± 2.9	3.4 ± 5.3	ns
	Longitudinal CL follow-up (years)	3.2 ± 1.1	3.2 ± 1.2	ns	2.5 ± 1.0	2.4 ± 1.0	ns
Tau	FTP Entorhinal cortex	1.15 ± .14	1.32 ± .15	**<0.001**	1.27 ± .18	1.63 ± .28	**<0.001**
	T+ Entorhinal cortex	22%	69%	**<0.001**	57%	95%	**<0.001**
	FTP slope Entorhinal cortex	.02 ± .04	.01 ± .05	ns	.02 ± .05	.02 ± .08	ns
	FTP Temporal MetaROI	1.18 ± .07	1.39 ± .17	**<0.001**	1.25 ± .12	1.74 ± .40	**<0.001**
	T+ Temporal MetaROI	13%	90%	**<0.001**	45%	98%	**<0.001**
	FTP slope Temporal MetaROI	.01 ± .04	.04 ± .06	**0.01**	.03 ± .04	.08 ± .01	**0.006**
	FTP Global ROI	1.08 ± .05	1.24 ± .09	**<0.001**	1.09 ± .05	1.42 ± .27	**<0.001**
	T+ Global ROI	0%	100%	–	0%	100%	–
	FTP slope Global ROI	.02 ± .04	.04 ± .06	**<0.001**	.06 ± .07	.01 ± .02	**<0.001**
	FTP slope follow-up time (years)	2.3 ± 1.1	2.4 ± 1.3	ns	2.1 ± 1.0	1.9 ± 0.8	ns
	CSF ptau181	27.5 ± 14.6	31.4 ± 11.8	ns	27.8 ± 10.3	38.0 ± 18.0	**<0.001**
	Plasma ptau181	17.1 ± 10.0	16.4 ± 8.04	ns	18.3 ± 9.88	21.0 ± 8.51	ns
Neurodegeneration	Hippocampal volume (adj)	7570 ± 800	7490 ± 703	ns	6890 ± 1070	6390 ± 919	**<0.001**
	Hippocampal volume slope (adj)	2.48 ± 1.08	2.15 ± .88	ns	2.10 ± .90	1.95 ± .87	ns

(Continues)

TABLE 1 (Continued)

		Unimpaired			Impaired		
		A+T−	A+T+	pval	A+T−	A+T+	pval
	N	119	49		96	133	
	Plasma NfL	41.9 ± 22.1	38.7 ± 23.4	ns	48.3 ± 29.0	46.5 ± 14.7	ns
	FDG	1.28 ± .12	1.33 ± .10	0.06	1.17 ± .14	1.11±.16	0.006
	MMSE	29.0 ± 1.3	28.9 ± 1.3	ns	26.8 ± 2.9	24.6 ± 4.2	<0.001
	MMSE slope	−0.1 ± .8	−0.3 ± 1.0	ns	−0.8 ± 1.7	−2.0 ± 2.8	<0.001
Cognition	PACC	0.3 ± 2.7	0.7 ± 3.0	0.04	−7.8 ± 5.2	−12.5 ± 7.5	<0.001
	PACC slope	−0.3 ± 1.0	−0.6 ± 1.5	ns	−1.4 ± 2.6	−3.1 ± 4.0	0.002
	Longitudinal cognitive follow-up (years)	3.2 ± 1.2	3.2 ± 1.4	ns	2.7 ± 1.3	2.2 ± 1.1	ns

Note: *p*-values that meet a Bonferroni-corrected criterion are underlined. **Nonmissing data for T−/T+ unimpaired individuals**. *APOE4* 108/46, Longitudinal FTP 64/27, CSF 56/24, plasma 44/25, longitudinal hippocampal slope 77/26, FDG 49/24, longitudinal amyloid PET 85/34, longitudinal PACC 94/36.**Nonmissing data for T−/T+ impaired individuals**. *APOE4* 84/115, Longitudinal FTP 50/63, CSF data 43/60 , plasma 39/47, long hipp slope 62/75, FDG 86/115, longitudinal amyloid PET 62/75, longitudinal PACC 73/95.

Abbreviations: Aβ, amyloid-β; ADNI, Alzheimer's Disease Neuroimaging Initiative; *APOE4*, apolipoprotein E4; CSF, cerebrospinal fluid; EMCI, Early Mild Cognitive Impairment; FDG, fluorodeoxyglucose PET; FTP, [18F] flortaucipir; LMCI, Late Mild Cognitive Impairment; MMSE, Mini-Mental State Examination; NfL, neurofilament light; PACC, Preclinical Alzheimer's Cognitive Composite; PET, positron emission tomography, ROI, region of interest; URG, underrepresented racial group.

composite score with the following predictors: age, sex, body mass index, systolic blood pressure, antihypertensive medication use, smoking, and diabetes status.[29]

We also used clinical interview medical records to determine Modified Hachinski scores and the presence/absence of self-reported hypertension, hyperlipidemia, and diabetes, the number of cardiovascular conditions, and the number of overall health conditions from among the following categories: psychiatric, neurologic/noncognitive, head/eyes/ears/nose/throat, cardiovascular, respiratory, hepatic, dermatologic/connective tissue, musculoskeletal, endocrine-metabolic, gastrointestinal, hematopoietic/lymphatic, renal/genitourinary, allergies/drug sensitivities, smoking/alcohol/drug use, malignancy, cognitive disorder.

White matter hyperintensities (WMH) were quantified using previously validated methods.[30,31] All segmentation is initially performed in standard space resulting in probability likelihood values of WMH at each voxel in the white matter thresholded at 3.5 SD above the mean to create a binary WMH mask. Further segmentation is based on a modified Bayesian approach that combines image likelihood estimates, spatial priors, and tissue class constraints based on prior probability maps for WMH created from more than 700 individuals with semi-automatic detection of WMH followed by manual editing. The segmented WMH masks are then back-transformed into native space for tissue volume calculation.

We adjusted WMH for head size by regressing out the relationship between natural log-transformed WMH and ICV using the ICV mean of 283 Aβ− healthy controls and the slope of the WMH and total intracranial volume relationship[20]:

$$WMH_{adj} = \ln(WMH + 1) - (0.00040241(ICV - 1432.55)).$$

2.9.2 | α-synuclein

We categorized 75% (301/400) of participants who had a lumbar puncture as α-synuclein+/− based on a synuclein seed amplification assay carried out in the Amprion Clinical Laboratory (CLIA ID No. 05D2209417; CAP No. 8168002). When multiple CSF samples per participant were taken over time, the most recent was chosen for analysis (mean lumbar puncture and baseline tau PET time interval = 0.2 ± 2.9years; see Supplementary Figure). This assay detects misfolded α-synuclein aggregates in CSF and peripheral tissues and has been described in detail elsewhere.[32] A positive result indicates that α-synuclein aggregates were detected, consistent with Type 1 seeds seen in Parkinson's disease (PD) and Lewy body dementia (LBD) or with Type 2 seeds seen in multiple system atrophy (MSA), while a negative result reflects the absence of such aggregates. An indeterminate result occurs when a determination cannot be made after a sample is tested twice.

2.10 | Statistical methods

The amount of available data varied across measures; nonmissing data for each variable are listed in Table 1.

2.10.1 | Comparison of A+T− and A+T+ groups

Unimpaired and impaired A+T− and A+T+ groups were compared on demographic, comorbid disease, AD biomarker (Aβ, tau, neurodegeneration), and cognitive measurements using independent-samples

t tests (continuous variables) and chi-square tests (categorical variables) at $\alpha = 0.05$. For longitudinal measurements, annualized slopes were calculated using all available time points.

2.10.2 | Prediction of cognitive performance

Regression models were carried out in R and SPSS (v27) separately for unimpaired and impaired Aβ+ groups associating baseline cognitive outcomes (PACC, MMSE) with comorbidity predictors (FRS, α-synuclein+/− status), tau (global tau SUVr), tau and comorbidity interactions (global tau × FRS, global tau × α-synuclein), as well as age at baseline PET, sex, underrepresented racial group (URG) status (+/−), apolipoprotein E (*APOE*) ε4 status (+/−), and education.

2.10.3 | Tau regionwise analysis for A+T− and A+T+ groups

Finally, we examined regionwise baseline FTP SUVrs and SUVr slopes averaged across A+T− and A+T+ groups for 70 FreeSurfer-defined regions (see Supplementary Materials). Regional tau SUVrs were ranked for each individual (region rank 1 = highest SUVr, region rank 70 = lowest SUVr), then the median rank for each region was determined within each A+T− and A+T+ unimpaired and impaired group. The same procedure was carried out to rank regional SUVr slopes.

3 | RESULTS

3.1 | Aβ+ individuals with tau PET in the normal range

Of the entire sample with available Aβ and tau PET scans ($N = 890$), there were 397 Aβ+ individuals. Of this group, 64% of unimpaired and 20% of impaired individuals had entorhinal tau within the normal range, 65% of unimpaired and 24% of impaired individuals had normal temporal tau, and 71% of unimpaired and 42% of impaired individuals had normal global tau (Figure 1A). A total of 87% of the sample was concordant on tau status in the entorhinal and temporal metaROI regions (T+ on both or T− on both), and 88% was concordant on T+/− status in the temporal metaROI and global regions (Figure 1B).

3.2 | A+T− / A+T+ group comparisons based on global tau

To further explore T+ versus T− comparisons without regional bias in the Aβ+ sample, we used the global tau region to define T+/T− groups in subsequent analyses. We examined factors associated with low tau in unimpaired (119 A+T−, 49 A+T+) and impaired individuals (96 A+T−, 133 A+T+) by comparing A+T− to A+T+ groups with respect to demographic, health risk/comorbidities, AD biomarker, and cognitive variables (Table 1). Some data were missing, particularly for plasma biomarkers and longitudinal follow-up (see Table 1 footnote for nonmissing data for each variable).

Among individuals with available longitudinal tau PET data, 7/64 (11%) unimpaired A+T− and 12/50 (24%) impaired A+T− converted to A+T+ status (based on global tau) over an average of 2.2 ± 1.1 years of follow-up (also see Table 1 for slopes).

3.2.1 | Unimpaired A+T− versus A+T+ individuals

Compared to their A+T+ counterparts, unimpaired A+T− individuals had a smaller number of self-reported overall health conditions, had significantly higher PACC scores, and were less likely to report a subjective memory complaint, but did not differ significantly on age, sex, race, education, *APOE4*, or cardiovascular risk measures.

Of 126 unimpaired individuals with α-synuclein status data, 14/84 (17%) A+T− were α-synuclein+, a marginally smaller proportion compared to A+T+ individuals who were α-synuclein+ (13/42, 31%; $p = 0.055$). Of the α-synuclein+ results, all were consistent with Type 1 pathology (suggestive of LBD or PD) except for one A+T− individual with Type 2 pathology (consistent with MSA); there were no indeterminate samples.

On AD biomarkers, unimpaired A+T− individuals had lower Aβ (CLs), and, consistent with group definition, they had lower tau and lower tau slopes across most ROIs, but entorhinal cortex slopes did not differ significantly between groups. A+T− individuals had marginally greater hypometabolism but the groups did not differ significantly on hippocampal volume, on CSF or plasma ptau181, or on plasma NfL, though there were reduced sample sizes for some measures.

3.2.2 | Impaired A+T− versus A+T+ individuals

Compared to their A+T+ counterparts, impaired A+T− individuals were older, more likely to be male, self-identify as White, and had higher education, but the groups did not differ significantly on *APOE4*. The groups did not differ on overall health conditions or α-synuclein+ status.

Of 176 impaired individuals with α-synuclein status data, 18/69 (26%) A+T− were α-synuclein+, a proportion that did not differ from A+T+ individuals who were α-synuclein+ (31/107, 29%). All α-synuclein+ results were consistent with Type 1 pathology (LBD or PD) and there were no indeterminate samples.

A+T− individuals reported a significantly higher number of cardiovascular health conditions, had higher FRS values, were more likely to have hypertension, a modified Hachinski score greater than zero, and had marginally greater WMH. The A+T− group was less impaired on baseline entorhinal, temporal, and global tau PET, and had less tau accumulation longitudinally in temporal and global tau regions but not entorhinal cortex (Figure 2A). Baseline Aβ was also lower in the

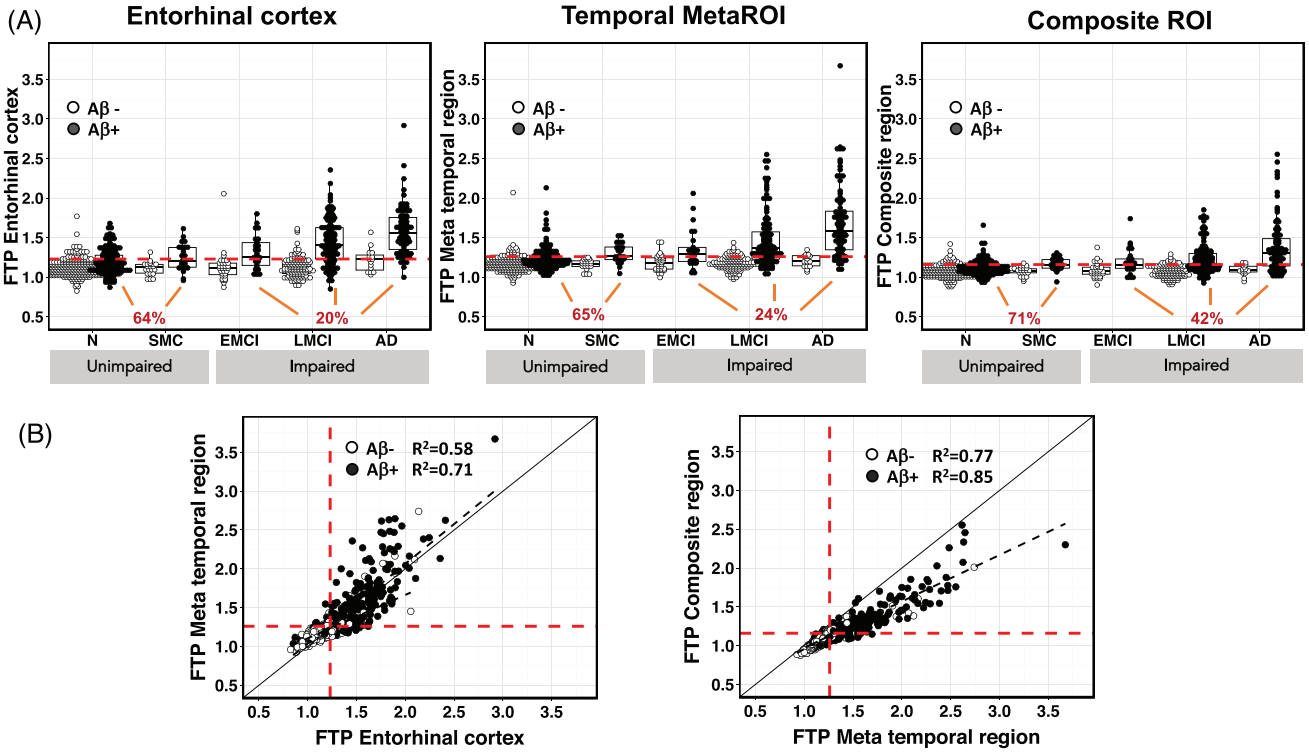

FIGURE 1 Tau PET SUVrs in ADNI participants. (A) Tau SUVr distributions for each region of interest are shown across ADNI unimpaired (N, cognitively unimpaired; SMC, subjective memory complaint) and impaired (EMCI, early mild cognitive impairment; LCMI, late mild cognitive impairment) participants. The red dotted lines represent the positivity threshold (90th percentile of the Aβ− cognitively unimpaired group). The percent of Aβ+ unimpaired and impaired individuals with tau in the normal (−) range of tau is shown for each region of interest. (B) Correlations are also shown between SUVrs for tau regions of interest across Aβ− and Aβ+ individuals. Aβ, amyloid-β; ADNI, Alzheimer's Disease Neuroimaging Initiative; FTP, [18F] flortaucipir; PET, positron emission tomography; SUVr, standard uptake value ratio.

A+T− group but longitudinal Aβ slopes did not differ between groups (Figure 2B). CSF ptau181, hippocampal volume, and hypometabolism were all less abnormal in the A+T− group, and baseline and longitudinal cognition was less impaired. Entorhinal cortical tau slope, hippocampal volume slope, plasma ptau, and plasma NfL did not differ significantly between groups.

3.3 | Predictors of cognitive performance

We examined whether comorbid disease or co-pathology, assessed with FRS and α-synuclein, and tau independently and/or jointly influenced cognition. There were separate regression models for unimpaired/impaired groups, for each tau region (entorhinal cortex, temporal metaROI, global cortical), and for each outcome (PACC, MMSE).

Among unimpaired Aβ+ individuals, the only significant predictor of higher PACC scores across all three models (for each tau region) was younger age. Tau, FRS, α-synuclein, tau × FRS, and tau × α-synuclein were not associated with PACC (model results not shown). We did not carry out regression models with MMSE as an outcome in unimpaired individuals because scores were >28 in 95% of individuals.

Among impaired Aβ+ individuals, low tau in each region of interested was consistently associated with higher PACC and MMSE scores. FRS and FRS × tau were not significant predictors of PACC or MMSE in any model (Table 2). The tau × α-synuclein interaction was significant in 5/6 models, and marginally significant in the remaining model, such that α-synuclein+ status was associated with poorer PACC and MMSE scores only when tau (across all three regions of interest) was low (Table 2, Figure 3).

3.4 | Tau regional rankings

We examined the ranked regional distributions of tau in 70 FreeSurfer-defined regions for each individual, then determined the median rank of each region for unimpaired and impaired A+T− and A+T+ groups. The regional pattern of the resulting median regional rankings was comparable across A+T+ and A+T− unimpaired and impaired groups, with medial and lateral temporal regions consistently ranked highest (Figure 4A) despite the substantial differences in global tau SUVrs in T− versus T+ groups based on group definition. There were similar findings for tau SUVr slopes, with comparable ranked regional slopes between groups (Figure 4B). The regional pattern of high-ranked slopes differed from the regional pattern of high-ranked baseline tau in that medial temporal slopes were highly ranked in the unimpaired A+T− group only (see Supplementary Materials for complete region rank lists).

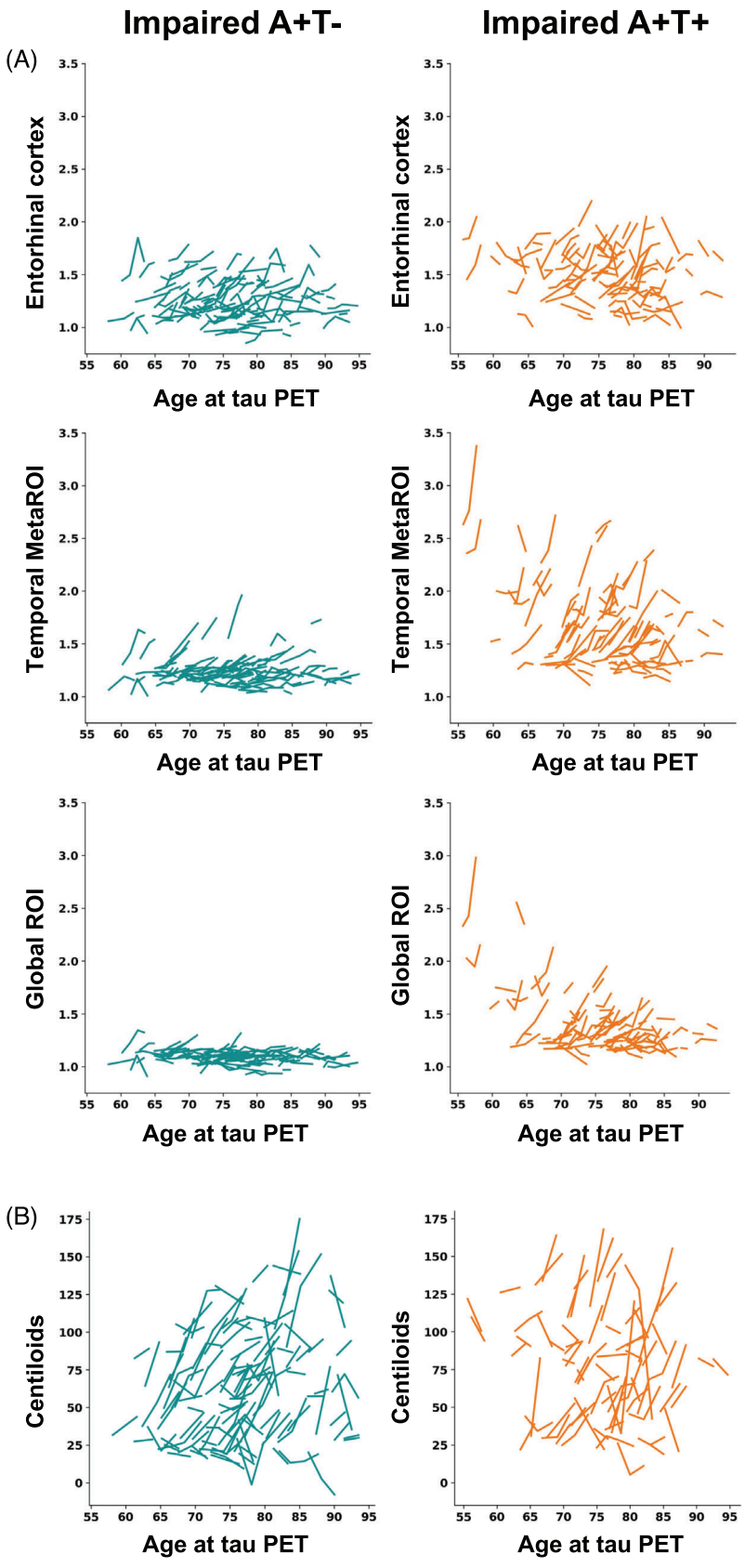

FIGURE 2 Tau and Aβ trajectories in Aβ+ impaired individuals. Descriptive plots of individual (A) raw tau PET SUVrs are shown for each ROI (entorhinal cortex; temporal metaROI; and the global region, which was used to define T+/− groups) and (B) centiloids as a function of age. Aβ, amyloid-β; PET, positron emission tomography; ROI, region of interest; SUVr, standard uptake value ratio.

TABLE 2 α-synuclein and tau are associated with cognitive performance in impaired Aβ+ individuals.

A. PACC outcome models							
					95% confidence interval		
Entorhinal cortex tau model	**Estimate**	**SE**	***t*-value**	***p*-value**	**lower**	**upper**	**partial η^2**
Intercept	4.37	7.45	0.59	0.559	−10.37	19.11	0.003
Sex (Female)	0.95	1.45	0.66	0.513	−1.91	3.81	0.003
Education	0.37	0.21	1.82	0.072	−0.03	0.78	0.024
APOE4 (−)	−0.77	1.07	−0.72	0.473	−2.88	1.35	0.004
Age	−0.13	0.06	−1.98	0.050	−0.26	0.00	0.028
FRS	−0.01	0.16	−0.08	0.937	−0.33	0.30	0.000
α-synuclein status (−)	11.45	5.17	2.22	**0.028**	1.23	21.67	0.035
Entorhinal cortex tau SUVr	−8.57	2.95	−2.90	**0.004**	−14.41	−2.73	0.059
Tau X FRS	0.01	0.11	0.13	0.898	−0.20	0.23	0.000
Tau X α-synuclein	−5.63	3.35	−1.68	0.096	−12.26	1.01	0.020
					95% confidence interval		
Temporal metaROI tau model	**Estimate**	**SE**	***t*-value**	***p*-value**	**lower**	**upper**	**partial η^2**
Intercept	12.29	6.50	1.89	0.061	−0.56	25.15	0.026
Sex (Female)	0.41	1.34	0.31	0.759	−2.24	3.06	0.001
Education	0.26	0.19	1.31	0.192	−0.13	0.64	0.013
APOE4 (−)	0.35	0.96	0.36	0.716	−1.55	2.25	0.001
Age	−0.22	0.06	−3.59	**<0.001**	−0.34	−0.10	0.087
FRS	−0.04	0.12	−0.36	0.721	−0.28	0.19	0.001
α-synuclein status (−)	11.56	3.72	3.11	0.002	4.21	18.92	0.067
Temporal metaROI tau SUVr	−7.56	1.96	−3.85	**<0.001**	−11.44	−3.68	0.099
Tau X FRS	0.03	0.08	0.44	0.658	−0.12	0.19	0.001
Tau X α-synuclein	−5.54	2.26	−2.45	**0.016**	−10.02	−1.06	0.042
					95% confidence interval		
Global tau model	**Estimate**	**SE**	***t*-value**	***p*-value**	**lower**	**upper**	**partial η^2**
Intercept	21.54	7.29	2.96	0.004	7.13	35.95	0.061
Sex (Female)	0.64	1.34	0.48	0.634	−2.01	3.29	0.002
Education	0.30	0.19	1.56	0.121	−0.08	0.69	0.018
APOE4 (−)	1.25	0.96	1.30	0.196	−0.65	3.15	0.012
Age	−0.31	0.07	−4.70	**<0.001**	−0.43	−0.18	0.141
FRS	−0.16	0.14	−1.11	0.271	−0.43	0.12	0.009
α-synuclein status (−)	15.63	4.27	3.66	**<0.001**	7.18	24.08	0.090
Global tau SUVr	−12.41	3.08	−4.04	**<0.001**	−18.49	−6.33	0.108
Tau X FRS	0.14	0.11	1.32	0.190	−0.07	0.36	0.013
Tau X α-synuclein	−9.81	3.14	−3.13	**0.002**	−16.01	−3.61	0.068
B. MMSE outcome models							
					95% confidence interval		
Entorhinal cortex tau model	**Estimate**	**SE**	***t*-value**	***p*-value**	**lower**	**upper**	**partial η^2**
Intercept	34.55	4.78	7.23	<0.001	25.11	44.00	0.279
Sex (Female)	0.53	0.93	0.58	0.565	−1.30	2.37	0.002
Education	0.16	0.13	1.22	0.225	−0.10	0.42	0.011
APOE4 (−)	−0.71	0.69	−1.04	0.300	−2.07	0.64	0.008
Age	−0.07	0.04	−1.57	0.118	−0.15	0.02	0.018

(Continues)

TABLE 2 (Continued)

B. MMSE outcome models							
					95% confidence interval		
Entorhinal cortex tau model	**Estimate**	**SE**	***t*-value**	***p*-value**	**lower**	**upper**	**partial η^2**
FRS	−0.06	0.10	−0.62	0.539	−0.26	0.14	0.003
α-synuclein status (−)	5.39	3.31	1.63	0.106	−1.16	11.94	0.019
Entorhinal cortex tau SUVr	−5.28	1.89	−2.79	**0.006**	−9.02	−1.53	0.054
Tau X FRS	0.05	0.07	0.67	0.503	−0.09	0.19	0.003
Tau X α-synuclein	−2.79	2.15	−1.30	0.197	−7.04	1.46	0.012
					95% confidence interval		
Temporal metaROI tau model	**Estimate**	**SE**	***t*-value**	***p*-value**	**lower**	**upper**	**partial η^2**
Intercept	38.51	4.18	9.22	<0.001	30.25	46.77	0.386
Sex (Female)	0.25	0.86	0.29	0.772	−1.45	1.95	0.001
Education	0.10	0.13	0.78	0.438	−0.15	0.34	0.004
***APOE4* (−)**	−0.14	0.62	−0.23	0.816	−1.37	1.08	0.000
Age	−0.11	0.04	−2.88	**0.005**	−0.19	−0.04	0.058
FRS	−0.06	0.08	−0.85	0.399	−0.21	0.09	0.005
α-synuclein status (−)	5.97	2.39	2.50	**0.014**	1.25	10.70	0.044
Temporal metaROI tau SUVr	−4.56	1.26	−3.62	**<0.001**	−7.05	−2.07	0.088
Tau X FRS	0.05	0.05	0.93	0.357	−0.05	0.14	0.006
Tau X α-synuclein	−3.09	1.45	−2.12	**0.036**	−5.96	−0.21	0.032
					95% confidence interval		
Global tau model	**Estimate**	**SE**	***t*-value**	***p*-value**	**lower**	**upper**	**partial η^2**
Intercept	43.93	4.63	9.49	<0.001	34.77	53.08	0.400
Sex (Female)	0.38	0.85	0.45	0.657	−1.31	2.06	0.001
Education	0.12	0.12	1.00	0.318	−0.12	0.37	0.007
***APOE4* (−)**	0.34	0.61	0.55	0.581	−0.87	1.55	0.002
Age	−0.16	0.04	−3.85	**<0.001**	−0.24	−0.08	0.099
FRS	−0.14	0.09	−1.61	0.110	−0.32	0.03	0.019
α-synuclein status (−)	8.26	2.72	3.04	**0.003**	2.89	13.63	0.064
Global tau SUVr	−7.62	1.95	−3.90	**<0.001**	−11.48	−3.76	0.101
Tau X FRS	0.13	0.07	1.79	0.075	−0.01	0.26	0.023
Tau X α-synuclein	−5.47	1.99	−2.75	**0.007**	−9.42	−1.53	0.053

Note: Regression model results are shown for prediction of (A) PACC and (B) MMSE in impaired Aβ+ individuals. Separate models were fitted for each tau PET region of interest. Raw data representing interactions for each model are illustrated in Figure 3. Significant predictors are shown in bold, and those meeting a Bonferroni correction are underlined.

Abbreviations: Aβ, amyloid-β; ADNI, Alzheimer's Disease Neuroimaging Initiative; *APOE4*, apolipoprotein E4; FRS, Framingham Risk Score; MMSE, Mini-Mental State Examination; PACC, Preclinical Alzheimer's Cognitive Composite; SUVr, standard uptake value ratio.

4 | DISCUSSION

Although tau burden is a key predictor of cognitive impairment in individuals on the AD pathway, we found that 20% to 42% (depending on the region assessed) of Aβ+ cognitively impaired individuals had tau PET burden within the normal range, indicating that a substantial proportion of symptomatic patients on the AD pathway have an atypical biomarker signature (A+T−) that is characterized as "AD pathologic change" but does not meet NIA-AA criteria for AD. One explanation for low tau is an earlier stage of disease progression,[2,33] and this is consistent with some of our findings (lower Aβ, lower tau and neurodegeneration markers, better cognitive performance in A+T− individuals). But impaired A+T− individuals differed from their A+T+ counterparts in additional ways that are not consistent with earlier disease stage: they were more likely to be male, older, more highly educated, and had more cardiovascular disease (CVD) risk factors including higher FRS values, modified Hachinski scores, and WMH. They were also less likely to self-identify as belonging to a non-White

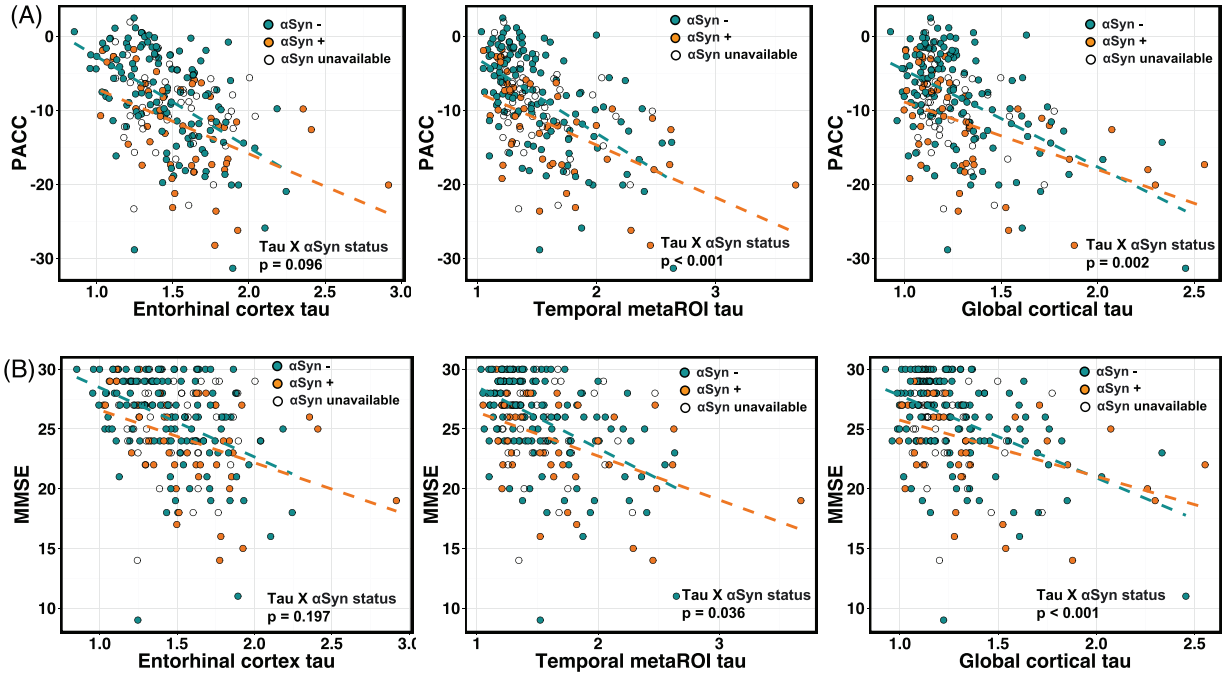

FIGURE 3 The effect of α-synuclein and tau on cognitive performance in Aβ+ impaired individuals. Raw data from (A) PACC scores and (B) MMSE scores are shown as a function of each tau region of interest for α-synuclein ± groups. Statistical significance of tau by α-synuclein interaction term is shown based on regression models (see Methods); full linear regression model results appear in Table 2. Aβ, amyloid-β; MMSE, Mini-Mental State Examination; PACC, Preclinical Alzheimer's Cognitive Composite.

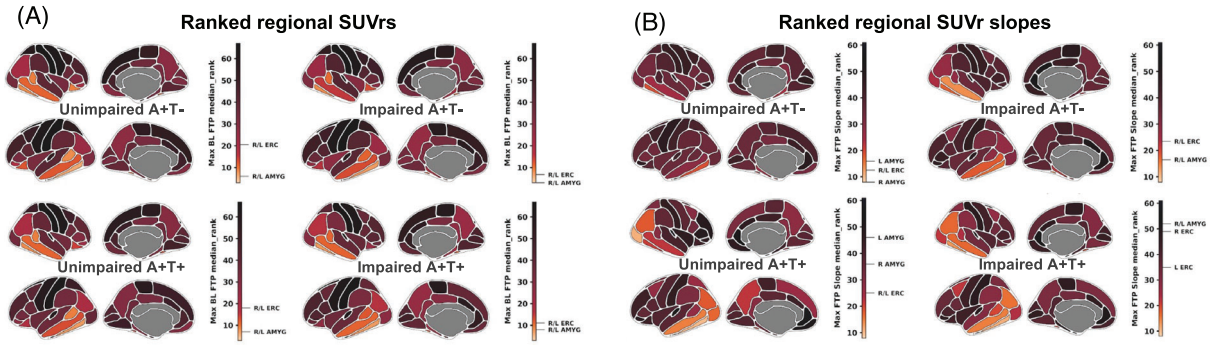

FIGURE 4 Regional tau SUVrs and ranked regional tau in Aβ+ high and low tau unimpaired and impaired groups. Brain renderings of 70 FreeSurfer-defined tau PET baseline regional median ranks (A) and ranked regional slopes (B) are shown for each unimpaired/impaired and high/low tau Aβ+ group. Medial temporal regions (entorhinal cortex, amygdala) were included in the mean calculations and ranking, but are not visible on the renderings, so their position is shown on the color bar for comparison with other regions. See Supplementary Materials for complete list of regional rankings. Aβ, amyloid-β; PET, positron emission tomography; SUVr, standard uptake value ratio.

racial group (ie, URG), although interpretation of this finding is limited by the small number of URG participants.

Also in the impaired group only, α-synuclein was linked to poorer cognition when tau is low, providing in vivo biomarker support for pathology evidence that mixed pathologies contribute to cognitive performance,[10,12] and also indicating that the toxic influence of tau may surpass that of other co-pathologies as tau burden increases. Tau and α-synuclein had additional independent effects on cognition, but the main effect of tau was more consistent and explained more variance than that of α-synuclein. This was true of all tau regions of interest, but the tau × α-synuclein interaction had the strongest effect on cognition in temporal and global regions of interest, consistent with a primary role for cortical tau burden in disease progression and cognitive symptoms.[34,35] Interestingly, although CVD was more prevalent in the A+T− impaired group, FRS was not associated with cognition in either the impaired or unimpaired groups, independently or as a joint predictor with tau.

Our findings extend previous work showing that tau can remain low for extended time periods despite Aβ positivity,[9] and are in agreement with recent evidence that approximately 50% to 65% of Aβ+ MCI and 8% to 20% of Aβ+ AD patients have entorhinal and temporal tau PET in the normal range, while larger proportions have normal

extratemporal neocortical tau.[8] Also consistent with our findings, T− status and lower tau accumulation over time has been associated with older age, male sex, less neurodegeneration assessed with cortical thickness in AD-specific regions (assessed with hippocampal volume and hypometabolism in our study), and less cognitive impairment.[5,6,8] Our findings are also consistent with neuropathology studies reporting that neurofibrillary tangles at autopsy are lower in men than women[7,36] and that pathology such as TDP-43, α-synuclein, and vascular pathology that frequently accompanies Aβ and tau but cannot be detected in vivo is common in clinically-diagnosed AD [11,37,38] and is more common in older than younger patients with clinical AD.[7] Although our ability to assess the full range of age-related neuropathologies (eg, TDP-43, FTLD-tau, pathology associated with small vessel disease) is limited by currently available in vivo biomarkers, α-synuclein may be representative of other co-pathologies on impairment, either via a direct effect on cognitive performance, or by increasing vulnerability to modest amounts of tau. The α-synuclein CSF seed amplification assay used in this study has been validated pathologically in PD and LBD, as well as, importantly, diffuse pathology in the context of diagnoses other than LBD,[32] suggesting that this assay is sensitive to α-synuclein observed in clinically-diagnosed AD patients such as those in ADNI, and has been linked to cognitive deficits even in unimpaired Aβ+/− individuals.[39]

Our findings also suggest that variability in tau burden may play a role in the efficacy of Aβ- and tau-modifying therapies. ADNI has targeted enrollment of individuals who would be likely to participate in a clinical trial of therapeutic AD treatment,[40] so the frequency of T− individuals in this study is likely to be representative of those in an Aβ- or tau-modifying treatment trial, contrasting with some tau PET studies with participants recruited from tertiary clinics who have early onset AD and/or atypical syndromes that may have disproportionately higher tau than is seen in the older population and drive associations between tau and cognitive performance.[41] Screening for the presence of Aβ and/or tau is increasingly used to ensure the presence of the therapeutic target, such as selecting participants with intermediate global tau in the donanemab phase 1 and 2 trials.[14,42] Our results suggest that individuals with lower tau may progress too slowly to respond to treatment or may have different characteristics and/or comorbidities that account for their impairment and that may make an Aβ- or tau-modifying treatment less effective.

Strengths of this study include the large sample of unimpaired and impaired individuals, and extensive biomarker, demographic, health, and cognitive phenotyping in a sample that is geographically diverse, though ADNI participants lack racial and ethnic diversity. There were also several limitations. First, although ADNI offers broad biomarker phenotyping compared to many observational studies, only a subset of individuals had longitudinal data and certain measurements (eg, plasma ptau181 and NfL, α-synuclein), limiting interpretation of findings related to these variables. Following the in-progress revised diagnostic criteria for AD,[4] more complete characterization of fluid (Core 1; "early") biomarkers such as plasma ptau 217 and 231 relative to PET (Core 2; "late") could provide information about whether there is early pathology in the A+T− group that is not detectable with PET but could nonetheless contribute to cognitive performance; the available (but limited) CSF ptau181 and plasma ptau181 findings are inconsistent, with CSF ptau181 indicating low tau in A+T− individuals and plasma ptau181 showing no difference between A+T− and A+T+ groups. The importance of comparing fluid to PET biomarker measurements is reinforced by reports that FTP PET signal is unlikely to be sensitive to early stages of tau burden at autopsy,[43,44] suggesting our assessment of tau in this study reflects significantly progressed pathology. This aligns with our observation that subthreshold tau in the A+T− individuals accumulates in a similar, temporal-predominant pattern as the A+T+ individuals, emphasizing the role of lateral temporal regions in Aβ-specific disease progression[45] and indicates that tau PET accumulates in an AD-like pattern that is suggestive of disease progression even when it is within the normal range.

A second limitation is that a survival effect may have contributed to our group differences, since individuals who are high in tau and other comorbidities may be less likely to participate in research studies or may not meet enrollment criteria. Third, findings may differ when using different methodological approaches to defining elevated tau, although tau regions of interest were highly inter-correlated, and our regression results were similar across these regions of interest. Finally, we did not use partial volume corrected data to define tau status; atrophy decreases tracer signal resulting in lower SUVrs, especially for older, symptomatic individuals, so non-partial volume corrected data is likely a conservative estimate of tau accumulation in this sample.

The pattern of characteristics associated with low tau in impaired but not unimpaired Aβ+ individuals suggests that before significant impairment is present, low tau in the presence of Aβ primarily reflects an earlier stage of disease. Once cognitive impairment is present, however, A+T− status is associated with a more complex, heterogeneous profile that cannot simply be explained by an earlier course of disease since it is more common in older individuals. Impairment in such individuals is driven by α-synuclein to a greater extent than tau or CVD. Although it is not currently possible to assess many other age-related co-pathologies in AD, α-synuclein is likely to be representative of these other co-pathologies in its influence on cognition in individuals on the AD pathway.

ACKNOWLEDGMENTS

We thank Jacinda Taggett for her help in study analyses. Data collection and sharing for this project was funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI) (National Institutes of Health Grant U01 AG024904). ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: Alzheimer's Association; Alzheimer's Drug Discovery Foundation; Araclon Biotech; BioClinica, Inc.; Biogen Idec Inc.; Bristol-Myers Squibb Company; Eisai Inc.; Elan Pharmaceuticals, Inc.; Eli Lilly and Company; Euroimmun; F. Hoffmann-La Roche Ltd and its affiliated company Genentech, Inc.; Fujirebio; GE Healthcare; IXICO Ltd.; Janssen Alzheimer Immunotherapy Research & Development, LLC.; Johnson & Johnson Pharmaceutical Research & Development LLC.; Medpace, Inc.; Merck & Co., Inc.; Meso Scale Diagnostics, LLC.; NeuroRx Research;

Neurotrack Technologies; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Piramal Imaging; Servier; Synarc Inc.; and Takeda Pharmaceutical Company. The Canadian Institutes of Rev December 5, 2013 Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health (www.fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Disease Cooperative Study at the University of California, San Diego. ADNI data are disseminated by the Laboratory for NeuroImaging at the University of Southern California. This work was also supported in part by the Intramural Research Program of the National Institute on Aging (NIA), and the Center for Alzheimer's and Related Dementias (CARD), within the Intramural Research Program of the NIA and the National Institute of Neurological Disorders and Stroke (AG000546).

CONFLICT OF INTEREST STATEMENT

J. Lee, A. Murphy, T. J. Ward, D. Tosun, C. DeCarli, T. M. Harrison, and R. A. Koeppe have no disclosures. S. M. Landau is on the DSMB for KeifeRx and the NIH IPAT study. She has received speaking honoraria from Eisai and IMPACT-A.D. S. L. Baker has served as a consultant for Genentech. D. J. Harvey has served as a consultant for NervGen. M. W. Weiner serves on Editorial Boards for *Alzheimer's & Dementia*, *MRI*, and *TMRI*. He has served on Advisory Boards for Acumen Pharmaceutical, ADNI, Alzheon, Inc., Biogen, Brain Health Registry, Cerecin, Dolby Family Ventures, Eli Lilly, Merck Sharp & Dohme Corp., National Institute on Aging (NIA), Nestle/Nestec, PCORI/PPRN, Roche, University of Southern California (USC), NervGen. He has provided consulting to Baird Equity Capital, BioClinica, Cerecin, Inc., Cytox, Dolby Family Ventures, Duke University, Eisai, FUJIFILM-Toyama Chemical (Japan), Garfield Weston, Genentech, Guidepoint Global, Indiana University, Japanese Organization for Medical Device Development, Inc. (JOMDD), Medscape, Nestle/Nestec, NIH, Peerview Internal Medicine, Roche, T3D Therapeutics, University of Southern California (USC), and Vida Ventures. He has acted as a speaker/lecturer to The Buck Institute for Research on Aging, China Association for Alzheimer's Disease (CAAD), Japan Society for Dementia Research, and Korean Dementia Society. He holds stock options with Alzheon, Inc., Alzeca, and Anven. The following entities have provided funding for academic travel: University of Southern California (USC), NervGen, ASFNR, and CTAD Congress. W. J. Jagust has served as a consultant to Biogen, Novartis, Lilly, and Clario. Author disclosures are available in the supporting information.

DATA AVAILABILITY STATEMENT

All data used in this manuscript are available to the public at the ADNI data repository at the Laboratory of Neuroimaging (http://adni.loni.usc.edu.). Derived data are available from the authors upon request.

CONSENT STATEMENT

All participants gave informed consent through their local IRBs prior to study participation.

REFERENCES

1. Jack CR Jr, 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. doi:10.1016/j.jalz.2018.02.018
2. Ossenkoppele R, Pichet Binette A, Groot C, et al. Amyloid and tau PET-positive cognitively unimpaired individuals are at high risk for future cognitive decline. *Nat Med*. 2022;28(11):2381-2387. doi:10.1038/s41591-022-02049-x
3. Strikwerda-Brown C, Hobbs DA, Gonneaud J, et al. Association of elevated amyloid and tau positron emission tomography signal with near-term development of Alzheimer disease symptoms in older adults without cognitive impairment. *JAMA Neurol*. 2022;79(10):975-985. doi:10.1001/jamaneurol.2022.2379
4. Revised Criteria for Diagnosis and Staging of Alzheimer's Disease: Alzheimer's Association Workgroup. https://aaic.alz.org/diagnostic-criteria.asp
5. Pontecorvo MJ, Devous MD Sr, Navitsky M, et al. Relationships between flortaucipir PET tau binding and amyloid burden, clinical diagnosis, age and cognition. *Brain*. 2017;140(3):748-763. doi:10.1093/brain/aww334
6. Smith R, Strandberg O, Mattsson-Carlgren N, et al. The accumulation rate of tau aggregates is higher in females and younger amyloid-positive subjects. *Brain*. 2020;143(12):3805-3815. doi:10.1093/brain/awaa327
7. Spina S, La Joie R, Petersen C, et al. Comorbid neuropathological diagnoses in early versus late-onset Alzheimer's disease. *Brain*. 2021;144(7):2186-2198. doi:10.1093/brain/awab099
8. Ossenkoppele R, Leuzy A, Cho H, et al. The impact of demographic, clinical, genetic, and imaging variables on tau PET status. *Eur J Nucl Med Mol Imaging*. 2021;48(7):2245-2258. doi:10.1007/s00259-020-05099-w
9. Josephs KA, Weigand SD, Whitwell JL. Characterizing amyloid-positive individuals with normal tau pet levels after 5 years: an ADNI study. *Neurology*. 2022;98(22):e2282-e2292. doi:10.1212/WNL.0000000000200287
10. Kapasi A, DeCarli C, Schneider JA. Impact of multiple pathologies on the threshold for clinically overt dementia. *Acta Neuropathol*. 2017;134(2):171-186. doi:10.1007/s00401-017-1717-7
11. Nelson PT, Dickson DW, Trojanowski JQ, et al. Limbic-predominant age-related TDP-43 encephalopathy (LATE): consensus working group report. *Brain*. 2019;142(6):1503-1527. doi:10.1093/brain/awz099
12. Boyle PA, Yu L, Leurgans SE, et al. Attributable risk of Alzheimer's dementia attributed to age-related neuropathologies. *Ann Neurol*. 2019;85(1):114-124. doi:10.1002/ana.25380
13. Jellinger KA. Alpha-synuclein pathology in Parkinson's and Alzheimer's disease brain: incidence and topographic distribution–a pilot study. *Acta Neuropathol*. 2003;106(3):191-201. doi:10.1007/s00401-003-0725-y
14. Sims JR, Zimmer JA, Evans CD, et al. Donanemab in early symptomatic Alzheimer disease: the TRAILBLAZER-ALZ 2 randomized clinical trial. *JAMA*. 2023. doi:10.1001/jama.2023.13239
15. Mummery CJ, Borjesson-Hanson A, Blackburn DJ, et al. Tau-targeting antisense oligonucleotide MAPT(Rx) in mild Alzheimer's disease: a phase 1b, randomized, placebo-controlled trial. *Nat Med*. 2023;29(6):1437-1447. doi:10.1038/s41591-023-02326-3
16. Young CB, Winer JR, Younes K, et al. Divergent cortical tau positron emission tomography patterns among patients with preclinical Alzheimer disease. *JAMA Neurol*. 2022;79(6):592-603. doi:10.1001/jamaneurol.2022.0676
17. Petersen RC, Aisen PS, Beckett LA, et al. Alzheimer's Disease Neuroimaging Initiative (ADNI): clinical characterization. *Neurology*. 2010;74(3):201-209. doi:10.1212/WNL.0b013e3181cb3e25
18. Landau SM, Fero A, Baker SL, et al. Measurement of longitudinal beta-amyloid change with 18F-florbetapir PET and standardized uptake

value ratios. *J Nucl Med*. 2015;56(4):567-574. doi:10.2967/jnumed.114.148981
19. Royse SK, Minhas DS, Lopresti BJ, et al. Validation of amyloid PET positivity thresholds in centiloids: a multisite PET study approach. *Alzheimer's Res Ther*. 2021;13(1):1-10.
20. Jack CR Jr, Petersen RC, Xu Y, et al. Rate of medial temporal lobe atrophy in typical aging and Alzheimer's disease. *Neurology*. 1998;51(4):993-999. doi:10.1212/wnl.51.4.993
21. Landau SM, Harvey D, Madison CM, et al. Comparing predictors of conversion and decline in mild cognitive impairment. *Neurology*. 2010;75(3):230-238. doi:https://doi.org/10.1212/WNL.0b013e3181e8e8b8
22. Baker SL, Maass A, Jagust WJ. Considerations and code for partial volume correcting [(18)F]-AV-1451 tau PET data. *Data Brief*. 2017;15:648-657. doi:10.1016/j.dib.2017.10.024
23. Jack CR Jr, 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. doi:10.1016/j.jalz.2016.08.005
24. Bittner T, Zetterberg H, Teunissen CE, et al. Technical performance of a novel, fully automated electrochemiluminescence immunoassay for the quantitation of beta-amyloid (1-42) in human cerebrospinal fluid. *Alzheimers Dement*. 2016;12(5):517-526. doi:10.1016/j.jalz.2015.09.009
25. Karikari TK, Pascoal TA, Ashton NJ, et al. Blood phosphorylated tau 181 as a biomarker for Alzheimer's disease: a diagnostic performance and prediction modelling study using data from four prospective cohorts. *Lancet Neurol*. 2020;19(5):422-433. doi:10.1016/S1474-4422(20)30071-5
26. Mattsson N, Andreasson U, Zetterberg H, Blennow K. Alzheimer's disease neuroimaging I. association of plasma neurofilament light with neurodegeneration in patients with Alzheimer disease. *JAMA Neurol*. 2017;74(5):557-566. doi:10.1001/jamaneurol.2016.6117
27. 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;12:189-198.
28. Donohue MC, Sperling RA, Salmon DP, et al. The preclinical Alzheimer cognitive composite: measuring amyloid-related decline. *JAMA Neurol*. 2014;71(8):961-970. doi:10.1001/jamaneurol.2014.803
29. D'Agostino RB Sr, Vasan RS, Pencina MJ, et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation*. 2008;117(6):743-753. doi:10.1161/CIRCULATIONAHA.107.699579
30. DeCarli C, Miller BL, Swan GE, et al. Predictors of brain morphology for the men of the NHLBI twin study. *Stroke*. 1999;30(3):529-536. doi:10.1161/01.str.30.3.529
31. Maillard P, Lu H, Arfanakis K, et al. Instrumental validation of free water, peak-width of skeletonized mean diffusivity, and white matter hyperintensities: markVCID neuroimaging kits. *Alzheimers Dement*. 2022;14(1):e12261. doi:10.1002/dad2.12261
32. Arnold MR, Coughlin DG, Brumbach BH, et al. alpha-Synuclein Seed amplification in CSF and brain from patients with different brain distributions of pathological alpha-synuclein in the context of co-pathology and Non-LBD diagnoses. *Ann Neurol*. 2022;92(4):650-662. doi:10.1002/ana.26453
33. Sperling RA, Mormino EC, Schultz AP, et al. The impact of amyloid-beta and tau on prospective cognitive decline in older individuals. *Ann Neurol*. 2019;85(2):181-193. doi:10.1002/ana.25395
34. Chen SD, Lu JY, Li HQ, et al. Staging tau pathology with tau PET in Alzheimer's disease: a longitudinal study. *Transl Psychiatry*. 2021;11(1):483. doi:10.1038/s41398-021-01602-5
35. Biel D, Brendel M, Rubinski A, et al. Tau-PET and in vivo Braak-staging as prognostic markers of future cognitive decline in cognitively normal to demented individuals. *Alzheimers Res Ther*. 2021;13(1):137. doi:10.1186/s13195-021-00880-x
36. Oveisgharan S, Arvanitakis Z, Yu L, Farfel J, Schneider JA, Bennett DA. Sex differences in Alzheimer's disease and common neuropathologies of aging. *Acta Neuropathol*. 2018;136(6):887-900. doi:10.1007/s00401-018-1920-1
37. Farfel JM, Yu L, Boyle PA, et al. Alzheimer's disease frequency peaks in the tenth decade and is lower afterwards. *Acta Neuropathol Commun*. 2019;7(1):104. doi:10.1186/s40478-019-0752-0
38. Rabinovici GD, Carrillo MC, Forman M, et al. Multiple comorbid neuropathologies in the setting of Alzheimer's disease neuropathology and implications for drug development. *Alzheimers Dement* 2017;3(1):83-91. doi:10.1016/j.trci.2016.09.002
39. Palmqvist S, Rossi M, Hall S, et al. Cognitive effects of Lewy body pathology in clinically unimpaired individuals. *Nat Med*. 2023;29(8):1971-1978. doi:10.1038/s41591-023-02450-0
40. Weiner MW, Veitch DP, Aisen PS, et al. The Alzheimer's disease neuroimaging initiative 3: continued innovation for clinical trial improvement. *Alzheimers Dement*. 2017;13(5):561-571. doi:10.1016/j.jalz.2016.10.006
41. Scholl M, Lockhart SN, Schonhaut DR, et al. PET Imaging of tau deposition in the aging human brain. *Neuron*. 2016;89(5):971-982. doi:10.1016/j.neuron.2016.01.028
42. Mintun MA, Lo AC, Duggan Evans C, et al. Donanemab in early Alzheimer's disease. *N Engl J Med*. 2021;384(18):1691-1704. doi:10.1056/NEJMoa2100708
43. Fleisher AS, Pontecorvo MJ. Positron Emission Tomography imaging with [18F]flortaucipir and postmortem assessment of Alzheimer disease neuropathologic changes. *JAMA Neurol*. 2020;77(7):829-839. doi:10.1001/jamaneurol.2020.0528
44. Moscoso A, Wren MC, Lashley T, et al. Imaging tau pathology in Alzheimer's disease with positron emission tomography: lessons learned from imaging-neuropathology validation studies. *Mol Neurodegener*. 2022;17(1):39. doi:10.1186/s13024-022-00543-x
45. Insel PS, Young CB, Aisen PS, et al. Tau positron emission tomography in preclinical Alzheimer's disease. *Brain*. 2023;146(2):700-711. doi:10.1093/brain/awac299

SUPPORTING INFORMATION

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

How to cite this article: Landau SM, Lee JQ, Murphy A, et al. Individuals with Alzheimer's disease and low tau burden: Characteristics and implications. *Alzheimer's Dement*. 2024;1-15. https://doi.org/10.1002/alz.13609

APPENDIX

ADNI COINVESTIGATORS

Name	Location	Role	Contribution
Michael W. Weiner, MD	University of California, San Francisco	Principal Investigator	PI
John Q. Trojanowski, MD, PhD	University of Pennsylvania	Core Leader	Coordinated Biomarker Core
Leslie Shaw, PhD	University of Pennsylvania	Core Leader	Coordinated Biomarker Core
Laurel Beckett, PhD	University of California, Davis	Core Leader	Coordinated Biostatistics Core
Paul Aisen, MD	University of Southern California	Core Leader	Coordinated Clinical Core
Ronald Petersen MD, PhD	Mayo Clinic	Core Leader	Coordinated Clinical Core
Andrew J. Saykin, PsyD	Indiana University	Core Leader	Coordinated Genetics Core
Arthur W. Toga, PhD	University of Southern California	Core Leader	Coordinated Informatics Core
Clifford Jack, MD	Mayo Clinic, Rochester, Minnesota	Core Leader	Coordinated MRI core
John C. Morris, MD	Washington University	Core Leader	Coordinated neuropathology Core
William Jagust, MD	University of California, Berkeley	Core Leader	Coordinated PET Core

Note: Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at:.
http://adni.loni.usc.edu/wpcontent/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.