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FEATURED ARTICLE

Traumatic brain injury and post-traumatic stress disorder are not associated with Alzheimer's disease pathology measured with biomarkers

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Abstract

Introduction: Epidemiological studies report an association between traumatic brain injury (TBI) and post-traumatic stress disorder (PTSD) and clinically diagnosed Alzheimer's disease (AD). We examined the association between TBI/PTSD and biomarker-defined AD.

*Deceased

Methods: We identified 289 non-demented veterans with TBI and/or PTSD and controls who underwent clinical evaluation, cerebrospinal fluid (CSF) collection, magnetic resonance imaging (MRI), amyloid beta (Aβ) and tau positron emission tomography, and apolipoprotein E testing. Participants were followed for up to 5.2 years.

Results: Exposure groups (TBI, PTSD, and TBI + PTSD) had higher prevalence of mild cognitive impairment (MCI: $P < .0001$) and worse Mini-Mental State Examination scores (PTSD: $P = .008$; TBI & PTSD: $P = .009$) than controls. There were no significant differences in other cognitive scores, MRI volumes, Aβ or tau accumulation, or in most longitudinal measures.

Discussion: TBI and/or PTSD were not associated with elevated AD biomarkers. The poorer cognitive status of exposed veterans may be due to other comorbid pathologies.

KEYWORDS
Alzheimer's disease, amyloid, cerebrovascular disease, cognitive decline, head injury, neurodegeneration, post-traumatic stress disorder, tau, traumatic brain injury, veterans

1 | INTRODUCTION

Traumatic brain injury (TBI) is associated with long-term consequences including cognitive impairment and neurological disease.[1] A history of moderate to severe TBI has been associated with an approximate doubling of the risk of all-cause dementia.[2–4] Post-traumatic stress disorder (PTSD) is a psychiatric disorder that may follow exposure to traumatic stress including military combat.[5] Like TBI, PTSD has been associated with the development of dementia in later life[6,7] although evidence for this association is mixed.[8,9] TBI and PTSD are commonly comorbid.[10]

Many epidemiological studies[2] investigating cognitive sequelae of TBI or PTSD have reported associations with all-cause dementia and with Alzheimer's disease (AD). AD, a progressive cognitive disorder initially causing mild cognitive impairment (MCI)[11] and ultimately leading to dementia, is among the pathologies for up to 80% of dementia cases[12] and is therefore an important candidate for the pathological outcome of both TBI and PTSD. A meta-analysis[4] of 32 studies reported head injury was associated with a relative risk (RR) of 1.63 (95% confidence interval [CI]: 1.34–1.99) for all-cause dementia, and 1.49 (95% CI: 0.91–2.43) for AD, and recent large cohort studies[3,13,14] reported similar associations. There is variable evidence for PTSD as a risk factor for MCI/dementia. A meta-analysis of seven studies calculated a pooled hazard ratio (HR) of 1.55 (1.41–1.81) for dementia after PTSD[15] and a recent large study reported that individuals with PTSD exposure had a HR of 1.36 (1.12–1.67) for AD, and 1.80 (1.40—2.31) for vascular neurodegenerative diseases.[16] Conversely, a smaller meta-analysis[8] and a recent study[9] found no associations between PTSD and subsequent dementia. Almost all previous studies suggesting that TBI and PTSD are risk factors for dementia/AD have been hampered by methodological issues including limited sample size; variability in clinical diagnosis of dementia/AD; and poorly defined, self-reported TBI[17,18] and PTSD.[19] While self-reporting of TBIs occurring decades earlier can capture exposures that did not result in clinical evaluation and subsequent medical records, it may also be inaccurate due to impairment of recollection from the injury[18] and difficulty encoding events around the injury particularly during military combat. A combination of self-report TBI and medical records therefore has the highest likelihood of capturing all TBIs.

As most research on PTSD, TBI, and risk of dementia has relied on clinical diagnosis, the biological mechanism underlying this increased risk is not understood. AD is biologically defined based on the presence of abnormal amyloid beta (Aβ) plaques and tau tangles and disease severity may be additionally characterized by neurodegeneration.[20] However, clinical and neuropathological diagnoses are not always concordant,[21] and a variety of in vivo biomarkers including Aβ positron emission tomography (PET), tau PET, measurements of abnormal Aβ and tau in cerebrospinal fluid (CSF), and brain magnetic resonance imaging (MRI) have now been shown to be closely associated with AD pathology.[22] Cerebrovascular disease markers such as white matter hyperintensities (WMHs) are also associated with cognitive impairment and play a complex role in the clinical expression of AD and related dementias.[23]

We tested the hypothesis that non-demented veteran elders with TBI and/or PTSD have elevated AD and cerebrovascular pathology compared to their veteran counterparts without lifetime TBI and/or PTSD, using the framework of the Alzheimer's Disease Neuroimaging Initiative (ADNI).[24] We measured AD pathology using in vivo measurements of Aβ (^{18}F-florbetapir) and tau (^{18}F-flortaucipir) PET, CSF $A\beta_{42}$, total tau (t-tau), and phosphorylated tau (p-tau)$_{181}$, and MRI. As the high frequency of abnormal AD biomarkers in participants with dementia would have required an impractically large sample size to detect an effect of TBI or PTSD on these biomarkers, we elected to exclude these veterans. We also measured cerebrovascular disease with WMHs measured on MRI. This study was conducted in 289 veterans with a history of TBI before, during, or after the Vietnam War

RESEARCH IN CONTEXT

1. **Systematic Review**: The authors used traditional (PubMed, Web of Science, etc.) sources to review the literature pertaining to the question of whether traumatic brain injury (TBI) and/or post-traumatic stress disorder (PTSD) is associated with Alzheimer's disease (AD) defined by biomarkers in veterans.
2. **Interpretation**: In this cohort study of 289 non-demented Vietnam veterans, exposure to TBI and/or PTSD was associated with a higher prevalence of mild cognitive impairment but not with elevated AD biomarkers. Poorer cognition in veterans exposed to TBI and/or PTSD is not caused by AD and may be due to other causes.
3. **Future Directions**: This article used cerebrospinal fluid and positron emission tomography biomarkers to define AD. Recently developed plasma biomarkers may allow a more cost-effective examination of larger and more diverse cohorts with a greater power to detect effects. Future studies may also investigate the underlying causes of the cognitive sequelae of TBI and PTSD.

and/or subsequent ongoing PTSD, and controls, and updates previously reported preliminary results.[25] Because the accumulation of Aβ precedes clinical AD diagnosis by 10 to 20 years,[26] we examined non-demented veterans to determine whether there was any evidence for AD-specific pathological change linked to subtle cognitive deficits that precede clinical dementia diagnosis. The relatively young age of Vietnam veterans (Table 1) and corresponding low frequency of clinically diagnosed dementia in this group made it a useful sample to determine whether TBI or PTSD increases the appearance of abnormal AD pathophysiology prior to the clinical diagnosis of dementia.

2 | METHODS

2.1 | Identification, screening, enrollment, and assessment of study subjects

Study recruitment is illustrated in Figure 1. Between 2013 and 2020 we identified non-demented US Vietnam veterans with a service-connected traumatic head injury and/or ≥1 moderate/severe TBI or TBI-related diagnostic code and/or ongoing PTSD, and controls from military and Veterans Benefits Administration records and in response to advertisements. Details of recruitment are provided in Section S1 in supporting information. Our goal was to cast a wide net for capturing TBIs in Vietnam veterans. The Glasgow Coma Scale was not available during the Vietnam conflict and the military medical personnel categorization of closed TBIs not requiring neurosurgery was variable. Thus, we used search terms, definitions, and diagnostic codes of that period that might appear in the accessible medical records. We used an operational definition of TBI consisting of non-penetrating head injury with amnesia, and/or loss of consciousness for 5 minutes, and/or being dazed and confused for longer than 1 day and additionally searched for diagnostic codes potentially related to TBI such as post-trauma headache, brain hemorrhage, and traumatic brain disease (Table S1 in supporting information). Controls were demographically comparable and service-connected for conditions other than TBI-related injuries or PTSD (Table S2 in supporting information), and had no record of TBI or PTSD before, during, or after the Vietnam War.

We sent study invitation packets to veterans meeting initial criteria and living within 150 miles of 19 ADNI clinics and prescreened them by telephone after obtaining verbal consent to ensure that the TBI-related diagnostic codes were head injury related (Sections S2 and S3 in supporting information), to diagnose MCI, and to identify exclusions (Section S4 in supporting information). As enrollment of veterans with TBI or TBI + PTSD was challenging and as these individuals often had MRI contraindications, we allowed their MRI requirement to be waived. Head injuries before, during, and after the Vietnam War were identified using a version of the Ohio State University TBI Identification Method–Interview Form, which captured TBI exposure before, during, and after the Vietnam War. MCI was diagnosed using the Telephone Interview for Cognitive Status 11-item questionnaire and an adapted version of the Eight-Item Interview to Differentiate Aging and Dementia. Final MCI diagnosis was made by the study clinician during the in-person baseline and follow-up visits.

Veterans meeting inclusion criteria were mailed self-report questionnaires and a written consent form for a telephone psychiatric clinical interview. After reviewing self-report questionnaires, we conducted a telephone clinical evaluation to assess current and lifetime PTSD and to rule out drug and alcohol issues and/or psychosis. Remaining veterans, either cognitively unimpaired (CU) or with MCI, were placed into one of four groups: TBI only, PTSD only, TBI and PTSD, and controls (no TBI/PTSD). Types of TBI and age at TBI, military and combat experience, and overall combat experience by group are detailed in Tables S3, S4, and S5 in supporting information, respectively.

2.2 | Clinical evaluation

Study veterans were referred to ADNI sites for clinical consent and evaluation, final diagnosis of MCI, lumbar puncture for CSF collection, neuropsychological testing, and apolipoprotein E (*APOE*) ε4 and genetic testing using ADNI procedures as described previously (Section S5 in supporting information). A subset (Figure 1) was followed for up to 5.2 years.

MRI,[27] florbetapir-PET (10 mCi with 4 × 5 min frames acquired at 50–70 minutes post-injection) and flortaucipir-PET acquisition (10 mCi with 6 × 5 minute frames acquired at 75–105 minutes post-injection) imaging were carried out as previously described (adni.loni.usc.edu/methods/pet-analysis-method/pet-analysis). Briefly, hippocampal, amygdala, entorhinal, and parietal cortex volumes were determined using FreeSurfer (v.5.1) T1-weighted images by a single

TABLE 1 Participant characteristics by group

Variable	Control ($n = 71$)	PTSD ($n = 81$)	TBI ($n = 43$)	TBI & PTSD ($n = 94$)
Age, mean (SD), y	71.4 (5.8)	68.2 (3.3)	70.4 (5.4)	69.8 (3.1)
Education, mean (SD), y	16.1 (2.1)	14.5 (2.3)	16.0 (2.3)	14.8 (2.5)
Male, *n* (%)	71 (100)	80 (99)	43 (100)	93 (99)
Hispanic, *n* (%)	4 (6)	10 (12)	2 (5)	6 (6)
Race, *n* (%)				
Black	4 (6)	6 (7)	4 (9)	8 (8)
White	61 (86)	69 (85)	37 (86)	77 (82)
Other	6 (8)	6 (7)	2 (5)	9 (10)
American Indian/ Alaska native	1 (1.4)	1 (1.2)	0 (0.0)	2 (2.1)
Asian	3 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)
More than 1 race	1 (1.4)	4 (4.9)	2 (4.6)	6 (6.4)
Unknown	1 (1.4)	1 (1.1)	0 (0.0)	1 (1.1)
APOE ε4+, *n* (%)[a]	19 (27)	19 (24)	13 (32)	21 (25)
MCI, *n* (%)	2 (3)	16 (20)	9 (21)	24 (25)
Progress to MCI[b], *n* (%)	4 (6)	5 (8)	1 (3)	5 (6)

Abbreviations: *APOE*, apolipoprotein E; MCI, mild cognitive impairment; PTSD, post-traumatic stress disorder; SD, standard deviation; TBI, traumatic brain injury.
[a]*APOE* results are missing for 1 Control, 1 PTSD, 3 TBI, and 10 TBI & PTSD participants.
[b]Percentage calculated out of the cognitively unimpaired participants in each group.

processing site to minimize measurement bias and these volumes were normalized by intracranial volume.[28] WMHs were determined from T1 and fluid attenuated inversion recovery images using a semi-automated Bayesian approach and normalized by intracranial volume.[29]

PET quantification differed from the usual ADNI MRI-dependent pipeline and enabled MRI-free calculation of regions of interest allowing all available PET scans to be analyzed, even those of participants with contraindications to MRI.[30] Full details are available in the "UC Berkeley- MRI-free processing methods" file in the Department of Defense (DOD)-ADNI section of: https://ida.loni.usc.edu/. Briefly, florbetapir and flortaucipir images were spatially normalized to Montreal Neurological Institute (MNI) 152 space tracer-specific templates. Florbetapir cortical summary standardized uptake volume ratios (SUVRs) were calculated using the mean uptake from within frontal, temporal, parietal, precuneus, anterior striatum, and insula regions relative to whole cerebellum.[31] Flortaucipir entorhinal and temporal composite SUVRs[32] relative to inferior cerebellar cortex[33] were calculated in MNI 152-space and FreeSurfer–defined regions from 200 ADNI participants that were spatially normalized to MNI 152 space and averaged together.

Baseline assessments of DOD participants with MCI ($n = 49$; all male) with TBI, PTSD, and TBI+PTSD were compared to those of MCI male participants ($n = 317$) from the National Institutes of Health (NIH)-funded ADNI study. Follow-up assessments for clinical evaluation, neuropsychological testing, MRI, and tau (flortaucipir) PET scans were made for 77.2%, 77.8%, 43%, and 24.2% of participants, respectively. The low number of follow-up assessments for flortaucipir is due to the availability of tau PET for which funding was approved in September 2014.

2.3 | Statistical analysis

Our study was designed to have 80% power to detect a minimum difference in means of 0.55 standard deviations (SD), assuming 65 participants in each group, an α of 0.025, and a two-sided test. All groups but the TBI group exceeded this target sample size. For comparison of the TBI group with the control group, we have 80% power to detect a difference as small as 0.78 SD. Minimum detectable differences are larger for the imaging and CSF outcomes, for which sample sizes are smaller. We calculated means and SD for all continuous variables (age, education, MRI volumetrics, florbetapir and flortaucipir SUVR, neuropsychological tests, CSF biomarkers) and percentages for all categorical variables of interest (sex, race/ethnicity, diagnosis, *APOE* ε4 status). Analyses focused on all available data for each measure of interest. Primary comparisons of interest for all analyses were between each exposure group and the control group. In cross-sectional analyses, we compared demographic and clinical characteristics of groups using analysis of variance or Fisher's exact test, and MRI volumetrics and most neuropsychological scores using linear regression. Mini-Mental State Examination (MMSE) was

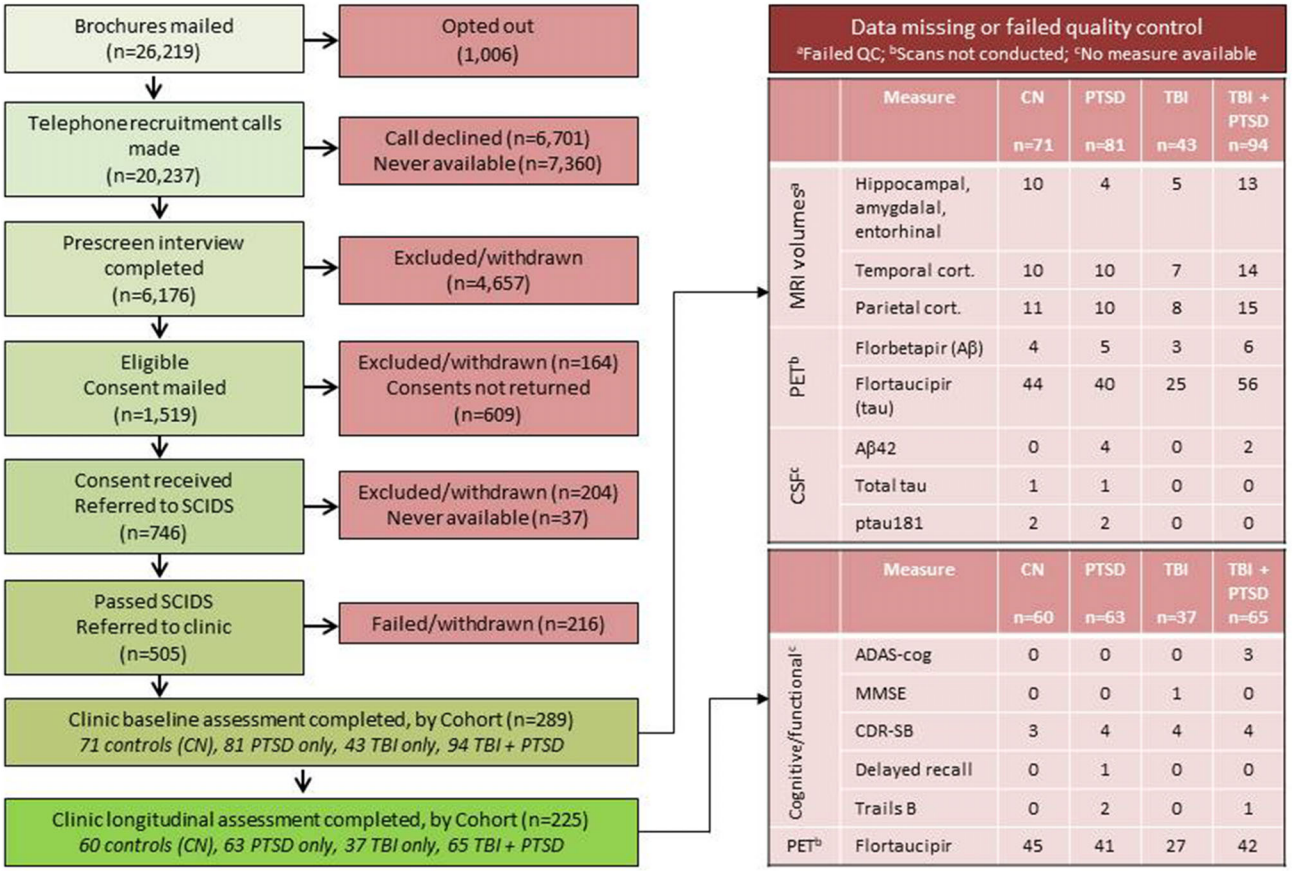

FIGURE 1 Flow of DOD ADNI recruitment and enrollment. Aβ, amyloid beta; ADAS-Cog; Alzheimer's Disease Assessment Scale–Cognitive subscale; ADNI, Alzheimer's Disease Neuroimaging Initiative; CDR-SB, Clinical Dementia Rating–Sum of Boxes; CN, control; cort., cortical; CSF, cerebrospinal fluid; DOD, Department of Defense; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; PET, positron emission tomography; PTSD, post-traumatic stress disorder; SCIDS, Structured Clinical Interview for DSM; TBI, traumatic brain injury; Trails B, Trail Making Test Part B

operationalized as the number of errors (30-MMSE). As Clinical Dementia Rating Sum of Boxes (CDR-SoB) scores and MMSE errors did not meet the assumptions of linear regression, we compared them using Poisson and negative binomial regression, respectively. WMH volumes were log-transformed to meet model assumptions. Aβ positivity determined using a threshold of 1.17 for florbetapir cortical SUVR was compared across groups using logistic regression. For comparison of change between groups, mixed effects models with a random intercept and slope, assuming an unstructured variance-covariance structure, were used. These methods assume missing assessments are missing completely at random. The interaction between exposure group and years since study start was of primary interest, because it captured differences between the groups in annual rates of change. All models were adjusted for age, education, *APOE* ε4 status, and baseline diagnosis of TBI/PTSD. Finally, to compare individuals with MCI exposed to TBI or PTSD (all males) with individuals known to be on the AD spectrum, age and *APOE* ε4 status adjusted comparisons between were made with ADNI MCI male participants on key AD markers and clinical indicators, using similar methods described above. We conducted all analyses using SAS software version 9.4 (SAS Institute Inc.) with a two-sided *P*-value < .05 considered statistically significant.

3 | RESULTS

3.1 | Demographic characteristics

Of 26,219 potential participants, 6176 completed the prescreening interview, 746 gave written consent and were referred to the structured telephone interview, 505 were referred to a clinic, and 289 were ultimately enrolled (Figures 1, S1-S3 in supporting information;Tables S6 and S7 in supporting information). These veterans were placed in four groups: PTSD ($n = 81$), TBI ($n = 43$), TBI & PTSD ($n = 94$), and controls (no TBI or PTSD; $n = 71$; Table 1). The PTSD group was younger, on average, than the control and TBI groups ($P < .05$). The PTSD and TBI & PTSD groups had fewer years of education than the other two groups ($P < .05$). There was a difference in frequency of MCI among the groups, with each of the exposure groups associated with higher frequency of MCI than the control group ($P < .001$). There was no significant difference between groups in participant sex ($P > .99$), Hispanic ethnicity ($P = .48$), race ($P = .96$), or *APOE* ε4 positivity ($P = .76$). Fourteen individuals progressed from CU to MCI during follow-up and none progressed from MCI to dementia; the percentage who progressed did not differ across groups ($P = .88$).

TABLE 2 Cognitive outcomes and biomarker levels at the initial assessment by group

Variable	Control ($n = 71$)	PTSD ($n = 81$)	TBI ($n = 43$)	TBI & PTSD ($n = 94$)	*P*-value[a]
ADAS-Cog total 13, mean (SD)	10.7 (4.6)	13.0 (4.1)	11.0 (4.2)	12.6 (5.4)	.04
MMSE, mean (SD)	28.8 (1.3)	28.0 (1.5)	28.5 (1.4)	27.9 (1.9)	.03
CDR SoB, mean (SD)	0.2 (0.4)	0.6 (0.8)	0.4 (0.6)	0.5 (0.8)	.11
Delayed Recall, mean (SD)	11.2 (3.8)	9.8 (3.8)	10.6 (3.5)	10.3 (4.1)	.64
RAVLT Sum of 5 trials, mean (SD)	41.5 (9.3)	39.0 (7.5)	40.5 (8.9)	39.1 (9.3)	.72
Trails B, mean (SD)	88.2 (42.0)	98.9 (45.1)	88.6 (37.6)	107.7 (55.1)	.18
Hippocampal volume, mean (SD), % of intracranial volume	0.51 (0.06)	0.53 (0.06)	0.52 (0.05)	0.51 (0.06)	.59
Amygdala volume, mean (SD), % of intracranial volume	0.21 (0.03)	0.22 (0.03)	0.21 (0.03)	0.21 (0.03)	.58
Entorhinal cortex volume, mean (SD), % of intracranial volume	0.26 (0.04)	0.28 (0.04)	0.27 (0.03)	0.27 (0.04)	.14
Temporal cortex volume, mean (SD), % of intracranial volume	5.8 (0.4)	5.9 (0.5)	5.9 (0.4)	5.9 (0.5)	.99
Parietal cortex volume, mean (SD), % of intracranial volume	6.3 (0.4)	6.3 (0.6)	6.3 (0.5)	6.3 (0.4)	.98
White matter hyperintensities volume, mean (SD)	5.3 (5.3)	4.6 (4.2)	5.4 (7.9)	4.9 (8.3)	.68
CSF Aβ42, mean (SD), pg/ml	1102.4 (558.7)	1325.6 (501.3)	1183.8 (562.4)	1240.7 (569.0)	.37
CSF t-tau, mean (SD), pg/ml	226.0 (95.9)	231.3 (107.5)	224.2 (87.4)	210.0 (79.7)	.49
CSF p-tau181, mean (SD), pg/ml	20.4 (10.1)	20.4 (12.2)	19.6 (8.6)	18.4 (7.1)	.31
Florbetapir cortical SUVR, mean (SD)	1.15(0.17	1.10 (0.12)	1.13 (0.18)	1.14 (0.16)	.37
Florbetapir positive (%)	28.4	13.2	22.5	29.5	.10
Flortaucipir entorhinal SUVR, mean (SD)	1.11 (0.11)	1.12 (0.15)	1.12 (0.10)	1.12 (0.14)	.96
Flortaucipir temporal SUVR, mean (SD)	1.17 (0.07)	1.16 (0.08)	1.18 (0.08)	1.16 (0.10)	.91

Note: Missing data:
CDR SoB: 2 Control, 4 PTSD, 3 TBI, 2 TBI & PTSD.
RAVLT: 1 PTSD.
Trails B: 3 PTSD, 1 TBI & PTSD.
Failed QC or no measurement provided from available sample:
Hippocampal volume: 10 Control, 4 PTSD, 5 TBI, 13 TBI & PTSD (failed QC).
Amygdala volume: 10 Control, 4 PTSD, 5 TBI, 13 TBI & PTSD (failed QC).
Entorhinal cortex volume: 10 Control, 4 PTSD, 5 TBI, 13 TBI & PTSD (failed QC).
Temporal cortex volume: 10 Control, 10 PTSD, 7 TBI, 14 TBI & PTSD (failed QC).
Parietal cortex volume: 11 Control, 10 PTSD, 8 TBI, 15 TBI & PTSD (failed QC).
Florbetapir PET: 4 Control, 5 PTSD, 3 TBI, 6 TBI & PTSD (scans not conducted).
Flortaucipir PET: 44 Control, 40 PTSD, 25 TBI, 56 TBI & PTSD (scans not conducted; scanning began in 2015).
CSF Aβ: 4 PTSD, 2 TBI & PTSD (no extrapolated value > 1700 available).
CSF tau: 1 Control, 1 PTSD (no measure from sample available).
CSF p-tau: 2 Control, 2 PTSD, 2 TBI & PTSD (no measure from sample available).
Abbreviations: Aβ, amyloid beta; ADAS-Cog, Alzheimer's Disease Assessment Scale-Cognitive subscale; *APOE*, apolipoprotein E; CDR-SoB, Clinical Dementia Rating, Sum of Boxes; CSF, cerebrospinal fluid; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; p-tau, phosphorylated tau; PTSD, post-traumatic stress disorder; QC, quality control; RAVLT, Rey Auditory Verbal Learning Test; SD, standard deviation; SUVR, standardized uptake volume ratio; TBI, traumatic brain injury; Trails B, Trail Making Test Part B; t-tau, total tau.
[a] *P*-value for an overall group comparison obtained from a model that adjusts for age, education, *APOE* ε4 status (ε4+ or ε4–), and diagnosis (Normal or MCI).

3.2 | Baseline assessments

At initial assessment (Table 2) no groups differed in Alzheimer's Disease Assessment Scale-13 item subscale (ADAS-Cog13) score after Tukey-Kramer adjustment for multiple comparisons, despite an overall group difference (overall difference: $P = .04$; pairwise comparisons: PTSD vs. controls: adjusted *P*-value = .08; PTSD vs. TBI: adjusted *P*-value = .11; all other comparisons had $P > .34$). The number of errors on MMSE differed between the groups ($P = .03$), with PTSD ($P = .008$) and TBI & PTSD ($P = .009$) groups having more errors than control group, both of which remained significant after the Tukey-Kramer adjustment for multiple comparisons. No other cognitive scores differed

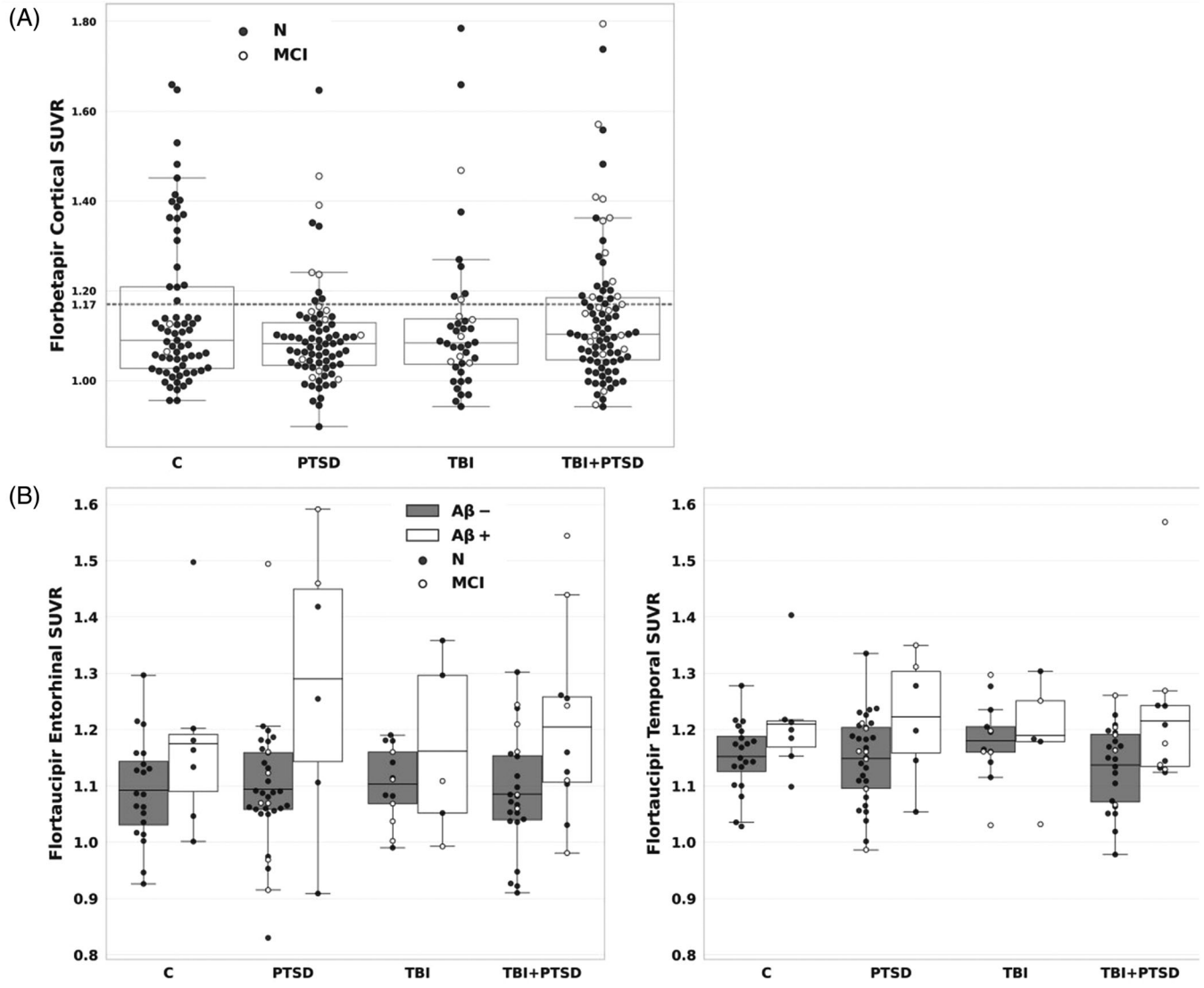

FIGURE 2 Florbetapir and flortaucipir binding by participant group. Florbetapir cortical SUVRs are shown for each participant group, with a dotted line reflecting the positivity threshold at 1.17 and separate points for cognitively normal and MCI individuals (A). Flortaucipir entorhinal cortex and temporal metaROI SUVRs are shown for each participant group by amyloid status, with separate points for cognitively normal and MCI individuals (B). C, controls; MCI, mild cognitive impairment; N, cognitively normal; PTSD, posttraumatic stress disorder; ROI, region of interest; SUVR, standardized uptake value ratio; TBI, traumatic brain injury

significantly between the groups. There were no significant differences between any groups in florbetapir or flortaucipir SUVR (Figure 2) nor in regional MRI volumes, WMH volume, and CSF biomarkers available for a subset of participants (Figure 1).

3.3 | Longitudinal assessments

A subset of veterans underwent longitudinal testing. We obtained an average of 2.3 longitudinal cognitive/functional assessments (SD = 0.6; range = 2–4) over an average of 1.8 years (SD = 1.1 years; range = 0.8–5.2 years) for estimation of annual rates of change (Table 3). These did not differ significantly between groups except for CDR-SoB, which worsened more in the TBI group than in the control group. We obtained longitudinal MRI for a subset of veterans over an average of 1.8 years (SD = 1.2 years; range = 0.9–5.2 years) with an average of 2.3 images per person (SD = 0.6; range = 2–5). Among 65-year-old CU veterans with 12 years of education and no *APOE* ε4 alleles, hippocampal volume (% total intracranial volume) significantly declined only in the TBI group by 0.01 (standard error [SE] = 0.004; $P = .01$). The difference in annual rates of change across groups did not reach significance ($P = .07$). There were no significant differences between the groups in rate of change in flortaucipir PET SUVR ($P > .30$), but due to the small sample size obtained (15 control, 22 PTSD, 10 TBI, and 23 TBI+PTSD) and variability in the measure of change, there was limited power to detect effects.

TABLE 3 Annual change by group in cognitive/functional measures

Variable	Control ($n = 60$)	PTSD ($n = 63$)	TBI ($n = 37$)	TBI & PTSD ($n = 65$)	*P*-value[a]
ADAS-Cog, mean (SD)	−0.02 (0.32)	−0.28 (0.26)	0.09 (0.42)	0.37 (0.33)	.29
MMSE, mean (SD)	−0.14 (0.14)	−0.22 (0.11)	−0.13 (0.19)	−0.13 (0.15)	.91
CDR SoB, mean (SD)	−0.05 (0.05)	−0.09 (0.04)	0.10 (0.07)	−0.07 (0.05)	.03
Delayed Recall, mean (SD)	0.71 (0.30)	0.33 (0.24)	0.51 (0.39)	0.55 (0.31)	.58
RAVLT Sum of 5 trials, mean (SD)	0.007 (0.80)	−0.59 (0.64)	−1.24 (1.01)	−0.34 (0.80)	.61
Trails B, mean (SD)	4.63 (3.39)	3.23 (2.75)	6.00 (4.48)	8.75 (3.55)	.49

Note: Annual change is estimated for a 65 year old cognitively unimpaired individual with 12 years of education and no *APOE* ε4 alleles. Annual change and the corresponding standard error are presented for each group.
Missing data:
ADAS-Cog: 3 TBI & PTSD.
MMSE: 1 TBI.
CDR SoB: 3 Control, 4 PTSD, 4 TBI, 4 TBI & PTSD.
Delayed Recall: 1 PTSD.
Trails B: 2 PTSD, 1 TBI & PTSD.
Abbreviations: ADAS-cog, Alzheimer's Disease Assessment Scale-Cognitive subscale; *APOE*, apolipoprotein E; CDR-SoB, Clinical Dementia Rating, Sum of Boxes; CSF, cerebrospinal fluid; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; PTSD, post-traumatic stress disorder; RAVLT, Rey Auditory Verbal Learning Test; TBI, traumatic brain injury; Trails B, Trail Making Test Part B.
[a]*P*-value for an overall group difference in rate of change.

3.4 | Comparison of DOD MCI participants with ADNI MCI participants

We compared the 49 DOD MCI participants (all male) to TBI, PTSD, and TBI & PTSD with those of 317 MCI male participants from the NIH-funded ADNI study to understand differences between MCI veterans selected for history of TBI and/or PTSD and ADNI MCI participants on the AD continuum (Table 4). DOD MCI participants were slightly younger with a lower frequency of at least one *APOE* ε4 allele than MCI in the NIH-funded study. They also had slightly lower MMSE scores and higher hippocampal volumes compared to ADNI MCI participants.

4 | DISCUSSION

In this study of Vietnam veterans exposed to TBI and/or PTSD, there was no evidence for increased AD or cerebrovascular pathology in any exposure group compared to unexposed controls despite the greater frequency of MCI in all exposure groups ($P < .001$), and the lower MMSE scores in the PTSD ($P = .008$) and TBI & PTSD ($P = .009$) groups. We did not detect any group differences in AD biomarkers including PET and CSF measurements of Aβ and tau, nor in neurodegeneration measured by hippocampal volume on MRI, or cerebrovascular disease measured with WMH. Longitudinally, there were no group differences in CSF or PET measures of Aβ or tau change over time and the sole change in cognition detected was a slightly a greater decline in CDR-SoB in the TBI only group compared to controls. Our results suggest that TBI or PTSD or TBI/PTSD together do not contribute to an increase or acceleration in AD biomarkers.

Our data showing comparable degree of abnormality in biomarkers of Aβ, tau, and neurodegeneration between exposure and control groups do not support the hypothesis that TBI and PTSD are associated with biomarker-defined AD. This is consistent with previous reports using biomarker or neuropathologically defined AD. Veterans with PTSD did not differ in Aβ and tau PET SUVR, or MRI volumes from those with no PTSD, despite having a lower Montréal Cognitive Assessment score.[34] Self-reported TBI with loss of consciousness was not associated with neuritic plaques or neurofibrillary tangles at autopsy in a pooled dataset from the Religious Orders Study (ROS), The Memory and Aging Project (MAP), and the Adult Changes in Thought (ACT) cohorts or in the National Alzheimer's Coordinating Center (NACC) cohort.[35] A history of self-reported mild TBI (mTBI) in 134 CU elders was not significantly associated with cortical Aβ burden or accumulation.[36] Conversely, a study reported a slight elevation of cortical tau but not Aβ in unimpaired and impaired participants with a self-reported history of head injury from ADNI and Indiana University Alzheimer's Disease Research Center.[37] Differences in TBI definitions and severity, and the use of unverified self-report data[17] together with a small sample size of more severely impaired participants may contribute to these inconsistencies. Nevertheless, the overall consistency of these studies with our results strengthens our conclusions.

Our major finding neither that TBI nor PTSD was associated with evidence of increased Aβ, tau or neurodegeneration biomarkers must be reconciled with the well-documented association of TBI and PTSD with increased frequency of dementia, often diagnosed clinically as AD. This discrepancy may be attributable to the fundamental differences between the biological definition of AD used in this study[20] that identifies underlying neuropathology, and the broader clinical and behavioral definition of AD dementia used in most epidemiological studies. The clinical diagnosis of AD dementia is based on clinical evaluations of

TABLE 4 Comparison of MCI male participants in the DOD- and NIH-funded studies

Variable	NIH male MCI	DOD male MCI	*P*-value[a]
Age, mean (SD), y	72.5 (7.1) ($n = 315$)	69.8 (3.7) ($n = 49$)	<.001
APOE ε4+, %	47.5 ($n = 301$)	20.4 ($n = 44$)	<.001
ADAS-Cog total 13, mean (SD)	16.1 (6.5) ($n = 316$)	15.1 (5.4) ($n = 49$)	.75
MMSE, mean (SD)	28.0 (1.7) ($n = 317$)	27.4 (2.1) ($n = 49$)	<.001
Florbetapir cortical SUVR, mean (SD)	1.22 (0.23) ($n = 286$)	1.19 (0.17) ($n = 42$)	.23
Florbetapir positive, %	55.2 ($n = 286$)	38.1 ($n = 42$)	.98
Hippocampus, mean (SD), % of intracranial volume	0.46 (0.08) ($n = 248$)	0.50 (0.07) ($n = 33$)	.03
White matter hyperintensities volume, mean (SD)	6.8 (9.1) ($n = 316$)	4.9 (5.2) ($n = 38$)	.85
CSF $A\beta_{42,}$ mean (SD), pg/ml	1034.0 (554.9) ($n = 291$)	1196.5 (550.5) ($n = 25$)	.67
CSF t-tau, mean (SD), pg/ml	260.3 (111.2) ($n = 291$)	263.0 (151.2) ($n = 25$)	.10
CSF p-$tau_{181,}$ mean (SD), pg/ml	25.1 (12.5) ($n = 291$)	25.2 (17.1) ($n = 24$)	.10

Abbreviations: ADAS-cog, Alzheimer's Disease Assessment Scale-Cognitive subscale; *APOE*, apolipoprotein E; CSF, cerebrospinal fluid; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; p-tau, phosphorylated tau; PTSD, post-traumatic stress disorder; SD, standard deviation; SUVR, standardized uptake volume ratio; TBI, traumatic brain injury; t-tau, total tau.

[a]Age and prevalence of the *APOE* ε4 allele was compared between groups using the two-sample t-test and chi-square test, respectively. All other variables were tested using a linear or generalized linear regression model adjusted for age and *APOE* ε4 status.

patients drawn from both community samples and specialty clinics over time with evolving diagnostic criteria related to cognitive symptoms and functional decline that interferes with daily activities, and may include a range of progressive neurodegenerative diseases.[38] Indeed, co-pathologies such as α-synuclein and TAR DNA-binding protein 43 are commonly found to accompany Aβ and tau at autopsy in patients with clinically diagnosed probable AD and MCI. TAR DNA-binding protein 43 has also been observed in chronic traumatic encephalopathy[39] which is associated with repetitive mild TBI.[40] The prevalence of of frontotemporal dementia (FTD) or Parkinson's disease (PD) dementia was also increased following TBI.[38] These studies support polypathology but not AD-specific pathology as a long-term outcome after TBI.[1] Similarly, various studies reported that PTSD was associated with an increased risk of FTD, PD/Lewy body dementia, and vascular dementia as well as AD,[6] and a large cohort study reported a greater increase in risk for vascular neurodegenerative diseases than for primary neurodegenerative diseases.[16] Therefore, reports of increased clinically diagnosed dementia as a result of TBI and/or PTSD in epidemiological studies likely reflect a broader range of pathologies.

Beyond the presence of other pathologies, additional mechanisms may account for the discrepancies between our results and previous epidemiological studies. TBI and PTSD may also lead to cognitive decline/dementia via reduced cognitive reserve,[41] non Aβ/tau mediated synaptic dysfunction, and/or neuroinflammation.[42] Synaptic dysfunction is implicated as an early pathological event in AD and may be the final common biological mechanism most proximal to neurodegeneration that links protein pathologies to disease symptoms.[42] Future studies may therefore examine changes of markers of synaptic function such as synaptosomal-associated protein 25kDa, neurogranin, postsynaptic density protein 95,[43] N-methyl D-aspartate receptor 2A[44] or neuroimaging markers such as synaptic vesicle glycoprotein 2A PET imaging,[45] as changes in this protein have been observed with TBI in mice.[46]

In contrast, MCI is a clinical rather than biological construct, and is considered the earliest clinical stage of AD and other dementias[11] although some patients do not progress to dementia. The higher frequency of MCI in veterans with TBI and PTSD in the absence of elevated Aβ and tau is consistent with the association of self-reported TBI with slightly increased odds of MCI after accounting for other factors such as depression and sex.[47] It could also be attributed to exacerbation of age-related decline,[48] the influence of cognitive reserve,[49] and non-Aβ and tau copathologies and/or synaptic dysfunction as discussed above.

Although exposure groups had a higher frequency of MCI and lower MMSE scores, they did not differ in auditory verbal learning, typically impaired early in AD progression (Table 3). This suggests that

these participants may have non-amnestic MCI (naMCI) characterized by deficits in other cognitive domains.[11] TBI was reported to impair processing speed and executive function,[50,51] but not memory[50-53] consistent with naMCI, although mTBI was additionally associated with impaired working memory and visual learning.[54] Veterans with PTSD had primarily impaired processing speed, executive function, and learning,[55] also consistent naMCI, which has a number of neurological sequelae distinct from AD including frontotemporal dementia, dementia with Lewy bodies, and vascular dementia,[11] and which may also be due to psychiatric problems.

Our lack of detection of Aβ was likely not attributable to the younger age of non-demented veterans compared to most studies of dementia, as Aβ begins to accumulate 10 to 20 years prior to symptom onset and approximately 30% of people in this age group have abnormal levels. Our study suggests that PTSD and/or TBI do not contribute to this accumulation. However, acute moderate or severe TBI has been associated with elevated levels of amyloid precursor protein, Aβ, and associated enzymes, as well as hyperphosphorylated microtubule-associated tau and associated enzymes, but it is unknown whether these changes are transient or ultimately lead to accumulation of AD neuropathology.[56] Such short-term changes would not be captured by our study methodology. It is also possible that the radiotracers used in this study were not sensitive to Aβ and tau accumulation that is specific to TBI and PTSD, as recent work has suggested that the currently available radiotracers are only minimally sensitive to detecting pathology in TBI and chronic traumatic encephalopathy.[57]

The use of biomarkers to define AD in this study circumvents the limitations of previous epidemiological reports of both TBI and PTSD which have been hampered by clinical AD and dementia phenotypes that do not align with biomarker and neuropathological evidence in a substantial proportion of patients.[21] Our use of medical records to determine TBI history overcomes the documented unreliability of self-report for TBI.[18] However, self-report of TBI was also necessary as many veterans who experienced TBI during Vietnam service were not admitted to hospitals, and no contemporary records of TBI while deployed to Vietnam are available. Although we are confident that our methodologies capture the vast majority of TBIs, it is possible that controls had unreported exposures to blasts or head impacts during training. It is also possible that alternative definitions of TBI may have changed our results. This study was not epidemiologically sampled. Written consent was received from only 3.7% of veterans who were initially contacted and up to 75% of veterans were excluded at different points. Some did not return for follow-up assessments due to health issues, travel challenges, or lack of interest (Figures S1 and S2). Despite our efforts, the number of Black and Hispanic veterans who enrolled was low relative to their proportions in the veteran population. Additionally, up to 20% of participants' MRI scans failed quality control, and tau PET data were available for only 46% (N = 124) participants due to later availability of this modality. Therefore, the number of participants and scans limited the statistical power to test the underlying hypothesis. Due to the difficulty in enrolling veterans, we were unable to analyze impacts of TBI severity and number, or of the influence of medical comorbidities known to affect cognition such as vascular risk factors and depression, although there were no group differences in measures of vascular risk factors (Table S8 in supporting information). Difficulties in recruitment also resulted in the enrollment of only two women; therefore, we cannot extend our results to female veterans.

Consistent with epidemiological studies of TBI and PTSD, we observed increased cognitive impairment and prevalence of MCI in exposure groups. However, in contrast to studies based on clinically diagnosed AD dementia, neither TBI nor PTSD were associated with AD biomarkers of Aβ, tau, and neurodegeneration, or with WMH, a finding consistent with other biomarker or neuropathological studies.[34,35,58] This information raises questions about alternative mechanisms underlying cognitive symptoms and AD diagnosis in these patients.

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CONFLICTS OF INTEREST

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SUPPORTING INFORMATION

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

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