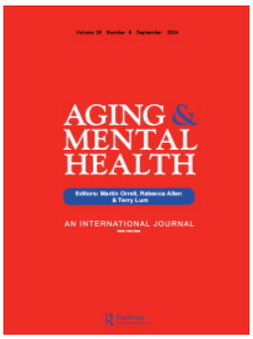

Routledge
Taylor & Francis Group

Aging & Mental Health

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/camh20

PTSD moderates the association between subjective cognitive decline and Alzheimer's disease biomarkers in older veterans

Britney Luu, Katherine J. Bangen, Alexandra L. Clark, Alexandra J. Weigand, Peter Rantins, Mary Ellen Garcia, Uriel Urias, Victoria C. Merritt, Kelsey R. Thomas & for the Department of Defense Alzheimer's Disease Neuroimaging Initiative

To cite this article: Britney Luu, Katherine J. Bangen, Alexandra L. Clark, Alexandra J. Weigand, Peter Rantins, Mary Ellen Garcia, Uriel Urias, Victoria C. Merritt, Kelsey R. Thomas & for the Department of Defense Alzheimer's Disease Neuroimaging Initiative (08 Aug 2024): PTSD moderates the association between subjective cognitive decline and Alzheimer's disease biomarkers in older veterans, Aging & Mental Health, DOI: 10.1080/13607863.2024.2389547

To link to this article: https://doi.org/10.1080/13607863.2024.2389547

Published online: 08 Aug 2024.

AGING & MENTAL HEALTH
https://doi.org/10.1080/13607863.2024.2389547

PTSD moderates the association between subjective cognitive decline and Alzheimer's disease biomarkers in older veterans

Britney Luu[a,b], Katherine J. Bangen[a,c], Alexandra L. Clark[d], Alexandra J. Weigand[e], Peter Rantins[a,b], Mary Ellen Garcia[a,c], Uriel Urias[a,b], Victoria C. Merritt[a,c,f], Kelsey R. Thomas[a,c] and for the Department of Defense Alzheimer's Disease Neuroimaging Initiative[*]

[a]VA San Diego Healthcare System, San Diego, CA, USA; [b]San Diego State University, San Diego, CA, USA; [c]Department of Psychiatry, University of California, San Diego, La Jolla, CA, USA; [d]Department of Psychology, University of Texas at Austin, Austin, TX, USA; [e]San Diego Joint Doctoral Program in Clinical Psychology, San Diego State University/University of California, San Diego, CA, USA; [f]Center of Excellence for Stress and Mental Health, VASDHS, San Diego, CA, USA

ABSTRACT

Objectives: Post-traumatic stress disorder (PTSD) and subjective cognitive decline (SCD) are independent risk factors for Alzheimer's disease (AD) and dementia, but the association of their interaction on AD biomarkers have yet to be characterized. This study aimed to examine the impact of PTSD on the association between SCD and tau and amyloid positron emission tomography (PET) as well as global cognition in older Veterans.

Method: This study included 87 Vietnam-Era Veterans without dementia (42 with PTSD; 45 without PTSD) from the Department of Defense-Alzheimer's Disease Neuroimaging Initiative. All participants had both tau and amyloid PET imaging as well as cognitive testing. SCD was measured using the Everyday Cognition questionnaire.

Results: While SCD was associated with tau PET, amyloid PET, and global cognition, PTSD moderated these associations for tau and amyloid PET levels. Specifically, Veterans without PTSD had a stronger positive relationship between SCD and AD biomarkers when compared to those with PTSD.

Conclusion: Higher SCD was associated with greater tau and amyloid burden and worse cognitive performance across the sample, though the tau and amyloid associations were stronger for Veterans without PTSD. Results highlight the potential benefit of comprehensive clinical assessments including consideration of mental health among older Veterans with SCD to understand the underlying cause of the cognitive concerns. Additionally, more work is needed to understand alternative mechanisms driving SCD in older Veterans with PTSD.

ARTICLE HISTORY
Received 28 February 2024
Accepted 1 August 2024

KEYWORDS
SCD; PTSD; veterans; Alzheimer's disease

Introduction

Post-traumatic stress disorder (PTSD) has been associated with increased risk of dementia (Yaffe et al., 2010). One recent meta-analysis found an adjusted hazard ratio (HR) of 1.55 for dementia in individuals with PTSD (Günak et al., 2020), and a large, population-matched study found stress-related disorders were associated with a HR of 1.36 for Alzheimer's disease (AD) and 1.80 for vascular neurodegenerative disease (Song et al., 2020). A different meta-analysis, however, did not find a relationship between PTSD and dementia (Kuring et al., 2020). Studies within young and middle-aged Veterans from the Iraq/Afghanistan wars have shown mixed results in whether Veterans with PTSD show poorer neuropsychological performance compared to those without PTSD (Merritt et al., 2019). However, recent work using data from the Department of Defense-Alzheimer's Disease Neuroimaging Initiative (DoD-ADNI) as well as studies on older, Vietnam-Era Veterans with PTSD more consistently identify poorer cognitive performances in those with PTSD relative to older Veterans without PTSD (Prieto et al., 2022; Schuitevoerder et al., 2013; Vasterling et al., 2002; Weiner et al., 2023). Notably, despite demonstrating lower scores on cognitive measures, there is not strong evidence of elevated AD biomarkers in those with PTSD. Taken together, results suggest that PTSD may negatively impact cognitive functioning independent of AD processes in late life (Elias et al., 2021; Weiner et al., 2023).

Beyond objective cognition, Veterans with PTSD also frequently endorse subjective cognitive difficulties, and hyperarousal, which often manifests as difficulty concentrating/distractibility, and is considered a core feature of PTSD (American Psychiatric Association, 2013; Mattson et al., 2019). In recent years, subjective cognitive decline (SCD) has garnered significant attention as being associated with elevated amyloid and tau AD pathology (Amariglio et al., 2012; Buckley et al., 2017, 2019) and as a method for identifying those at risk for progressing to AD dementia (Chapman et al., 2023; Jessen et al., 2014). SCD is defined as self-experienced decline in cognition relative to previous cognitive functioning that is not due to an acute event, psychiatric difficulties, medical disorder, or substance use (Jessen et al., 2014). Within Veterans, however, SCD may have differential utility as a prognostic tool given the greater proportions of Veterans with psychiatric disorders such as PTSD that potentially contribute to SCD

CONTACT Kelsey R. Thomas kthomas@health.ucsd.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 analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

independent of an AD process (Kessler et al., 2005; Kulka et al., 1990). Research examining associations between subjective and objective cognition in Veterans with and without PTSD is quite limited, particularly in older, Vietnam-Era Veterans. Within Iraq/Afghanistan-era Veterans, one study showed that PTSD mediated the association between subjective and objective cognition (Mattson et al., 2019) and another study showed that Veterans with PTSD (PTSD alone or comorbid mild traumatic brain injury [mTBI] + PTSD) endorsed more persistent subjective distress, including related to their ability to work or pursue an education, despite performing similarly to the mTBI-only and combat control Veterans on objective measures of functioning (Merritt et al., 2019).

Although recent findings from DoD-ADNI have shown that participants with PTSD and/or TBI do not show elevated AD biomarkers such as amyloid and tau (Weiner et al., 2023), no studies have examined whether PTSD moderates the associations of SCD with tau and amyloid levels on positron emission tomography (PET). The inclusion of tau PET in addition to amyloid PET is a particular strength given the strong link between cognition and tau in prodromal and early stages of AD (Gordon et al., 2019; Ossenkoppele et al., 2016; Thomas et al., 2022; Weigand et al., 2020). Therefore, the primary goal of this study was to investigate the associations of subjective cognition with tau and amyloid PET levels as well as global cognitive performance and to determine if PTSD moderates these relationships. We hypothesized that the main effect of SCD would be associated with tau PET, amyloid PET, and global cognition, and our primary hypothesis was that the association between SCD and tau and amyloid PET levels would be weaker in older Veterans with PTSD relative to those without PTSD due to the AD-independent effects of PTSD on cognition. We hypothesized that those with both greater SCD and PTSD would have worse global cognitive performance.

Methods

Participants

Data used in this current study were obtained from the publicly available Brain Aging in Vietnam War Veterans/Department of Defense Alzheimer's Disease Neuroimaging Initiative (DoD-ADNI) database (adni.loni.usc.edu). The study is directed by principal investigator Dr. Michael Weiner of the San Francisco VA Medical Center and University of California, San Francisco. The overarching goals of the DoD-ADNI study are to characterize the long-term neural and behavioral consequences of TBI and/or PTSD. The main aims and methods of DoD-ADNI as well as up-to-date information can be found at www.adni-info.org. This research was approved by the institutional review boards of all participating sites within ADNI and written informed consent was obtained for all study participants.

The enrollment process and exclusion criteria for DoD-ADNI have been described elsewhere (Weiner et al., 2014, 2023). Briefly, Vietnam Veterans without dementia who were aged 60–90 years older were recruited from 2013 to 2020. DoD-ADNI recruited for Veterans with PTSD only, with a non-penetrating TBI history only, with both PTSD and TBI, and control participants without PTSD or TBI. Individuals were excluded from DoD-ADNI if they met criteria for dementia, had a history of psychosis or bipolar disorder or a neurologic condition (e.g. seizure disorder, stroke), a history of alcohol or substance abuse/dependence within past 5 years, the presence of metal implants or claustrophobia that would prevent participants from undergoing an MRI, and medical contraindications for lumbar puncture PET scan, or other procedures as part of the study.

There were 87 Vietnam War Veterans included in this study (42 with PTSD, 45 without PTSD) who had both tau and amyloid PET imaging, subjective and objective cognition data, and psychiatric symptom data. Included participants also had TBI status, apolipoprotein E (APOE) genotype, and blood pressure data available.

Measures

Subjective cognitive decline

The Everyday Cognition (ECog) measure is a 39-item questionnaire that was used to determine the degree of subjective cognitive decline (Farias et al., 2008). Participants rated their ability to perform everyday tasks relative to 10 years ago on a scale of 1 ('better or no change') through 4 ('consistently much worse'). These everyday tasks were divided into cognitive domains associated with the task. This included memory, language, visuospatial, planning, organization, and divided attention. The ECog total scores were based on the mean of all items and the ECog domain subscales were based on the mean of the items that go into that specific domain. Higher scores indicated more subjective cognitive and functional difficulties.

PTSD classification

Current and lifetime PTSD symptom severity was measured using the Clinician-Administered PTSD Scale - 4th edition (CAPS-IV). Consistent with the ADNI-DoD criteria used in prior studies, classification of current PTSD was defined as a current CAPS score > 40, whereas individuals with scores <40 did not meet DoD-ADNI criteria for PTSD (Weiner et al., 2014). Participants with a lifetime CAPS score >40, but who had a current score of <40 were not classified as having current PTSD.

Tau and amyloid PET

PET imaging using flortaucipir (AV-1451) was used to quantify tau burden. The details of data acquisition and processing of ADNI flortaucipir PET data are available at adni.loni.usc.edu. We examined a priori regions of interest (ROI) that correspond to Braak staging given the expected pattern of tau spread in typical AD (Braak & Braak, 1991). Braak I included the entorhinal cortex, Braak III/IV was a composite of regions that extending beyond the medial temporal lobe to the amygdala and other subcortical regions as well as the cortex of the inferior temporal lobe and parahippocampal gyrus (i.e. moderately progressed), and Braak V/IV was a composite of regions that extend beyond the temporal lobe into the frontal, parietal and occipital cortex (Landau et al., 2021). Braak stage II risks possible unreliable PET measurement given the susceptibility of the hippocampus to partial voluming and therefore was not examined in the current study per extant recommendations (Landau et al., 2021). Standardized uptake variable (SUV) ratios (SUVRs) were calculated by dividing the SUV for each ROI by the inferior cerebellar gray and values underwent partial volume correction using the geometric transfer method (Baker et al., 2017). On average, the tau PET scan was acquired within 17 months of the baseline visit (median = 6 months, range = 0–49).

Florbetapir (AV45) PET was used to measure amyloid burden. The details of data acquisition and processing of ADNI florbetapir PET data are available at adni.loni.usc.edu. A summary SUVR was calculated by dividing the mean uptake across 4

AD-vulnerable cortical regions (frontal, anterior/posterior cingulate, lateral parietal, and lateral temporal cortices) by whole cerebellar (white and gray matter) uptake. Greater retention of florbetapir is reflective of a greater cortical Aβ load. On average, the amyloid PET scan was within 0.55 months of the baseline visit (median = 0 months, range = 0–21).

Global cognition

Six neuropsychological measures in the domains of memory, attention/executive functioning, and language were used to create a global cognition composite score (Rantins et al., 2024). Memory measures included the immediate and delayed recall scores from the Rey Auditory Verbal Learning Test and the Wechsler Memory Scale–Revised Logical Memory; measures of attention/executive functioning included Trail Making Test, Parts A and B total time; and measures of language included the total correct scores from the 30-item Boston Naming Test and Animal Fluency. The global composite score was created by converting raw scores to z-scores and taking the mean of all measures; the attention/executive measures z-scores were multiplied by −1 prior to being included in the global composite score, so higher scores indicated better performance for all measures.

Additional descriptive measures and covariates

The Clinical Dementia Rating (CDR) Global score at the baseline visit was used to determine proportion of participants considered cognitively unimpaired (score of 0) or to have mild cognitive impairment (score of 0.5; Morris, 1993). CDR scores of 1+ (i.e. consistent with dementia) were excluded. The CDR is a semi-structured interview that assesses difficulties across domains of Memory, Orientation, Judgment & Problem Solving, Community Affairs, Home & Hobbies, and Personal Care. TBI severity was included as a categorical variable and was based on the Veteran Affairs (VA)/DoD criteria 2021 Clinical Practice Guidelines (Department of Veterans Affairs & Department of Defense, 2021). Each TBI was coded, and the severity was based on the most severe TBI. An injury was classified as mild if the participant had a loss of consciousness (LOC) of <30 min, or alteration of consciousness (AOC) or post traumatic amnesia (PTA) of <24 h. The moderate and severe TBI classifications were combined since the information for PTA of >1 day was not available. Thus, an injury was classified as moderate-to-severe if the participants had LOC of >30 min, AOC of >24 h, or PTA of >1 day (Rantins et al., 2024). The Geriatric Depression Scale (GDS) was used to measure depressive symptom severity (Sheikh & Yesavage, 1986). Pulse pressure (systolic minus diastolic blood pressure) is considered a proxy for arterial stiffening and was included as a measure of vascular health (Nation et al., 2015). APOE ε4 genotype, based on whether a participant had 0 (non-carrier) or 1–2 (carrier) ε4 alleles, was included as a measure of genetic susceptibility to AD. While each identified race for this sample is included in Table 1 (Asian, Black/African American, white, more than one), due to the small number of Veterans who identified as a race other than white, race had to be coded as white or non-white for inclusion as a covariate in the models. Ethnicity was coded as Hispanic or non-Hispanic.

Statistical analyses

Independent samples t-tests and chi-squared tests were used to examine differences in demographic and clinical characteristics by PTSD status. General linear models were used to examine the association of SCD with PET neuroimaging and global cognition measures and the impact of PTSD on these associations. Given the non-normal distribution of tau and Aβ PET SUVRS, these variables were log-transformed prior to analyses. First, we examined the association between SCD (ECog) and tau PET (Braak I, Braak III/IV, Braak V/VI), amyloid PET, and global cognition when adjusting for age, education, depressive symptoms, pulse pressure, and PTSD status (Model 0). Next, Model 1 built on Model 0 by adding the SCD x PTSD status interaction to test whether PTSD status moderated the associations between SCD and the PET and global cognition measures while again including covariates of age, education, depressive symptoms, pulse pressure, PTSD status, and ECog in the model. Then, Model 2 included the same effects and covariates as Models 0 and 1 plus the covariates of APOE ε4 carrier status, race, ethnicity, and TBI severity status (none, mild, moderate-to-severe), which were added to determine if the results remained consistent in a more fully-adjusted model given that these variables could impact both amyloid and tau pathology, as well as subjective cognitive decline. Finally, sensitivity models were evaluated with the time between baseline assessment and PET scan as an additional covariate as well as when excluding for participants whose baseline visit was ≥24 months from their tau PET scan (all amyloid PET scans were <24 months from their baseline visit).

Results

Table 1 contains the descriptive demographic and clinical characteristics for the total sample and split by PTSD classification. On average, participants were approximately 70 years old, had 15 years of education, were 98% male, 91% white, and 9% Hispanic/Latinx. Roughly two-thirds of the sample had a Clinical Dementia Rating of 0 (cognitively unimpaired) and one-third had a CDR rating of 0.5 (consistent with mild cognitive impairment). Relative to Veterans without PTSD, Veterans with PTSD were younger ($p = 0.037$), had fewer years of education ($p = 0.039$), had greater depressive symptoms ($p < 0.001$), more current and lifetime PTSD symptoms ($p < 0.001$), and more severe subjective cognitive decline on the ECog ($p = 0.002$). Veterans without PTSD had greater tau burden for Braak I ($p = 0.050$) and Braak III/IV PET ($p = 0.007$) regional SUVRs. There was no difference in time interval between the initial visit when ECog was measured and PET scan dates by PTSD status.

General linear models examined the associations between SCD and AD PET and global cognition variables, as well as whether these relationships were moderated by PTSD status. In Model 0 which adjusted for age, education, depressive symptoms, pulse pressure, and PTSD status as covariates, there was a main effect of ECog total score on Braak I ($\beta = 0.395$, 95% CI [0.173, 0.616], $p < 0.001$, $\eta_p^2 = 0.136$), Braak III/IV ($\beta = 0.306$, 95% CI [0.085, 0.527], $p = 0.007$, $\eta_p^2 = 0.087$), Braak V/VI ($\beta = 0.289$, 95% CI [0.062, 0.515], $p = 0.013$, $\eta_p^2 = 0.074$), amyloid PET ($\beta = 0.258$, 95% CI [0.023, 0.493], $p = 0.032$, $\eta_p^2 = 0.058$), and global cognition ($\beta = -0.272$, 95% CI [−0.492, −0.052], $p = 0.016$, $\eta_p^2 = 0.070$) across the sample.

Next, Model 1 examined the PTSD x ECog interaction when it was added to Model 0 model (see Table 2). PTSD moderated the associations between ECog and Braak III/IV ($\beta = -0.228$, 95% CI [−0.453, −0.003], $p = 0.047$, $\eta_p^2 = 0.049$), Braak V/VI ($\beta = -0.260$, 95% CI [−0.489, −0.031], $p = 0.027$, $\eta_p^2 = 0.061$), and amyloid PET ($\beta = -0.262$, 95% CI [−0.497, −0.027], $p = 0.029$, $\eta_p^2 = 0.061$) such

Table 1. Characteristics of study sample and by PTSD status.

	Total sample ($N = 87$)	PTSD ($N = 42$)	No PTSD ($N = 45$)	p
Age, mean (SD)	69.82 (4.85)	68.71 (2.64)	70.84 (6.10)	.037
Education, mean (SD)	15.01 (2.55)	14.43 (2.40)	15.56 (2.60)	.039
Male, %	97.7%	2.4%	2.2%	.961
Hispanic/Latinx, %	9.4%	14.6%	4.5%	.111
Race				.999
Asian, %	2.3%	2.4%	2.2%	
Black/African American, %	4.6%	4.8%	4.4%	
White, %	90.8%	90.5%	91.1%	
More than one, %	2.3%	2.4%	2.2%	
MMSE, mean (SD)	28.11 (1.73)	27.90 (1.39)	28.31 (1.99)	.276
Global cognitive composite, mean (SD)	0.01 (0.80)	−0.12 (0.62)	0.13 (0.93)	.150
CDR global, 0/0.5, %	66.7%/33.3%	57.5%/42.5%	75.0%/25.0%	.089
GDS, mean (SD)	2.94 (3.19)	4.67 (3.43)	1.33 (1.83)	<.001
Current CAPS, mean (SD)	31.46 (26.79)	56.71(11.56)	7.89 (10.06)	<.001
Lifetime CAPS, mean (SD)	45.22 (33.82)	72.93 (19.66)	19.36 (21.42)	<.001
TBI History				.398
None, %	39.5%	42.9%	36.4%	
Mild, %	34.9%	38.1%	31.8%	
Moderate-to-severe, %	25.6%	19.0%	31.8%	
APOE ε4 carrier, %	25.8%	25.0%	28.6%	.715
Pulse pressure, mean (SD)	60.09 (14.21)	62.83 (13.68)	57.53 (14.37)	.082
ECog total, mean (SD)	1.67 (0.55)	1.89 (0.59)	1.52 (0.46)	.002
Tau Braak I PET SUVR, mean (SD)	1.45 (0.31)	1.38 (0.25)	1.51 (0.35)	.050
Tau Braak III/IV PET SUVR, mean (SD)	1.35 (0.14)	1.31 (0.11)	1.39 (0.15)	.007
Tau Braak V/VI PET SUVR, mean (SD)	1.43 (0.14)	1.41 (0.12)	1.45 (0.17)	.196
Amyloid PET SUVR, mean (SD)	1.08 (0.15)	1.05 (0.12)	1.11 (0.17)	.093
Amyloid PET positive, %	23.8%	16.7%	31.1%	.091

MMSE = Mini Mental State Exam; CDR = Clinical Dementia Rating; GDS = Geriatric Depression Scale; CAPS = Clinician Administered PTSD scale; TBI = traumatic brain injury; APOE = apolipoprotein E; ECog = Everyday Cognition scale.

that Veterans without PTSD had a stronger positive relationship between ECog and AD biomarker levels compared to those with PTSD. Specifically, relative to Veterans with PTSD, more severe SCD was associated with greater tau and amyloid in Veterans without PTSD. This moderation was not statistically significant for Braak I PET (β = −0.170, 95% CI [−0.398, 0.058], $p = 0.143$, $\eta_p^2 = 0.027$) or global cognition (β = 0.119, 95% CI [−0.109, 0.347], $p = 0.301$, $\eta_p^2 = 0.014$).

Model 2 then examined the same model as Model 1, but also included the additional covariates of APOE ε4 carrier status, race, ethnicity, and TBI status. These models were conducted to determine whether results remained consistent when adjusting for additional factors known to impact AD biomarkers and/or SCD. In these fully-adjusted models before the interaction was included, there was a main effect of ECog on Braak I (β = 0.377, 95% CI [0.140, 0.613], $p = 0.002$, $\eta_p^2 = 0.131$), Braak III/IV (β = 0.308, 95% CI [0.079, 0.537], $p = 0.009$, $\eta_p^2 = 0.097$), Braak V/VI (β = 0.275, 95% CI [0.039, 0.510], $p = 0.023$, $\eta_p^2 = 0.075$), and global cognition (β = −0.226, 95% CI [−0.438, −0.015], $p = 0.037$, $\eta_p^2 = 0.064$), but ECog was no longer significantly associated with amyloid PET (β = 0.245, 95% CI [−0.005, 0.496], $p = 0.055$, $\eta_p^2 = 0.057$). When the PTSD x ECog interaction was added, PTSD moderated the associations between ECog and Braak III/IV (β = −0.274, 95% CI [−0.518, −0.029], $p = 0.029$, $\eta_p^2 = 0.070$) and Braak V/VI (β = −0.283, 95% CI [−0.534, −0.031], $p = 0.028$, $\eta_p^2 = 0.071$) such that Veterans without PTSD had a stronger positive relationship between ECog and tau burden than those with PTSD (Figure 1). This moderation was not statistically significant for Braak I PET (β = −0.143, 95% CI [−0.403, 0.117], $p = 0.275$, $\eta_p^2 = 0.018$) or global cognition (β = 0.060, 95% CI [−0.174, 0.294], $p = 0.609$, $\eta_p^2 = 0.004$) and was no longer significant for amyloid PET in this model (β = −0.202, 95% CI [−0.476, 0.072], $p = 0.145$, $\eta_p^2 = 0.033$). The tau and amyloid PET models were re-evaluated with the time between baseline assessment and PET scan as a covariate and the pattern of results did not change.

Since 37 participants had their tau PET scan ≥24 months from their baseline evaluation (all amyloid PET scans were within <24 months), we also ran sensitivity tau PET analyses that included only the participants with tau PET within 24 months of their baseline visit ($n = 50$). Briefly, for Model 1, PTSD moderated the associations between ECog and Braak I (β = −0.367, 95% CI [−0.645, −0.089], $p = 0.011$, $\eta_p^2 = 0.145$), Braak III/IV (β = −0.410, 95% CI [−0.721, −0.099], $p = 0.011$, $\eta_p^2 = 0.145$), and Braak V/VI (β = −0.352, 95% CI [−0.689, −0.015], $p = 0.041$, $\eta_p^2 = 0.096$) such that Veterans without PTSD had a stronger positive relationship between ECog and tau PET levels compared to those with PTSD. For the fully-adjusted Model 2, PTSD still moderated the associations between ECog and Braak I (β = −0.374, 95% CI [−0.673, −0.076], $p = 0.016$, $\eta_p^2 = 0.179$) and Braak III/IV (β = −0.395, 95% CI [−0.729, −0.061], $p = 0.022$, $\eta_p^2 = 0.163$), but was no longer statistically significant for Braak V/VI (β = −0.323, 95% CI [−0.701, 0.055], $p = 0.091$, $\eta_p^2 = 0.092$).

Discussion

The present study sought to investigate the moderating effect of PTSD on the association between SCD and AD biomarkers measured using PET imaging as well as global cognition in older Vietnam-Era Veterans. Our study showed a significant association between SCD and tau PET levels across multiple brain regions, including Braak stages I, III/IV and V/VI. This suggests that greater subjective cognitive concerns are associated with higher tau burden in these regions, which represent both very early tau tangle accumulation as well as tau that has progressed well outside of the medial temporal lobe. Further, in the minimally adjusted model, SCD was also associated with amyloid PET levels, though this main effect of ECog was no longer significant in the fully adjusted model. The main effect of ECog was also significantly associated with global cognition measured using neuropsychological measures. These findings are in line with the growing recognition of SCD as a potential early marker of AD-related cognitive decline, particularly as it relates to tau burden (Jessen et al., 2014; Papp et al., 2020). While our results show that SCD is associated with greater tau, global cognition,

Table 2. Effects of subjective cognitive decline and PTSD on tau PET, amyloid PET, and global cognition.

	Braak I						Braak III/IV						Braak V/VI					
	Model 1			Model 2			Model 1			Model 2			Model 1			Model 2		
	β	se	*p*	β	se	*p*	β	se	*p*	β	se	*p*	β	se	*p*	β	se	*p*
Age	−0.006	.112	.954	−0.053	.138	.703	−0.009	.111	.034	−0.188	.130	.152	−0.188	.113	.100	−0.334	.133	.015
Education	0.083	.112	.461	0.068	.132	.607	−0.028	.110	.804	0.054	.124	.663	−0.031	.113	.785	0.003	.127	.979
GDS total	−0.179	.123	.149	−0.107	.143	.454	−0.216	.121	.009	−0.036	.134	.789	−0.183	.123	.142	−0.032	.138	.819
Pulse pressure	0.012	.107	.911	0.052	.132	.694	0.053	.106	.618	0.196	.125	.121	−0.074	.108	.494	−0.008	.128	.953
Hispanic				0.082	.128	.526				0.071	.121	.559				0.094	.124	.454
White				0.071	.137	.604				−0.023	.129	.861				−0.052	.132	.696
APOE ε4 carrier				0.027	.120	.826				0.005	.113	.966				0.098	.116	.403
No TBI (ref)	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Mild TBI				0.543	.267	.046				0.457	.252	.074				0.513	.259	.051
Mod/Sev TBI				0.152	.305	.621				−0.328	.287	.258				−0.145	.296	.624
PTSD	−0.258	.123	.039	−0.345	.153	.028	−0.323	.121	.009	−0.565	.144	<.001	−0.190	.123	.127	−0.359	.148	.018
ECog	0.444	.115	<.001	0.415	.123	.001	0.371	.114	.002	0.380	.116	.002	0.364	.166	.002	0.350	.119	.005
ECog x PTSD	−0.170	.115	.143	−0.143	.130	.275	−0.228	.113	.047	−0.274	.123	.029	−0.260	.115	.027	−0.283	.126	.028

	Amyloid						Global Cognition					
	Model 1			Model 2			Model 1			Model 2		
	β	se	*p*	β	se	*p*	β	se	*p*	β	se	*p*
Age	0.083	.116	.475	0.098	.143	.496	−0.265	.106	.021	−0.477	.124	<.001
Education	0.126	.116	.281	0.134	.134	.322	0.184	.112	.105	0.304	.119	.013
GDS Total	0.027	.132	.838	0.016	.151	.916	−0.058	.123	.638	−0.048	.128	.712
Pulse Pressure	0.121	.111	.281	0.063	.140	.657	0.019	.107	.858	0.134	.119	.266
Hispanic				−0.108	.136	.429				−0.208	.116	.077
White				−0.033	.159	.838				−0.098	.123	.432
APOE ε4 carrier				0.164	.127	.201				0.002	.108	.989
No TBI (ref)	–	–	–	–	–	–	–	–	–	–	–	–
Mild TBI				0.330	.274	.233				−0.020	.241	.935
Mod/Sev TBI				0.477	.324	.146				−0.816	.275	.004
PTSD	−0.277	.126	.031	−0.236	.158	.139	−0.046	.123	.707	−0.169	.138	.224
ECog	0.329	.119	.007	0.290	.128	.026	−0.306	.115	.010	−0.242	.111	.033
ECog x PTSD	−0.262	.118	.029	−0.202	.137	.145	0.119	.115	.301	0.060	.117	.609

GDS = Geriatric Depression Scale; APOE = apolipoprotein E; TBI = traumatic brain injury; Mod/Sev = Moderate-to-severe; PTSD = post-traumatic stress disorder; ECog = Everyday Cognition.

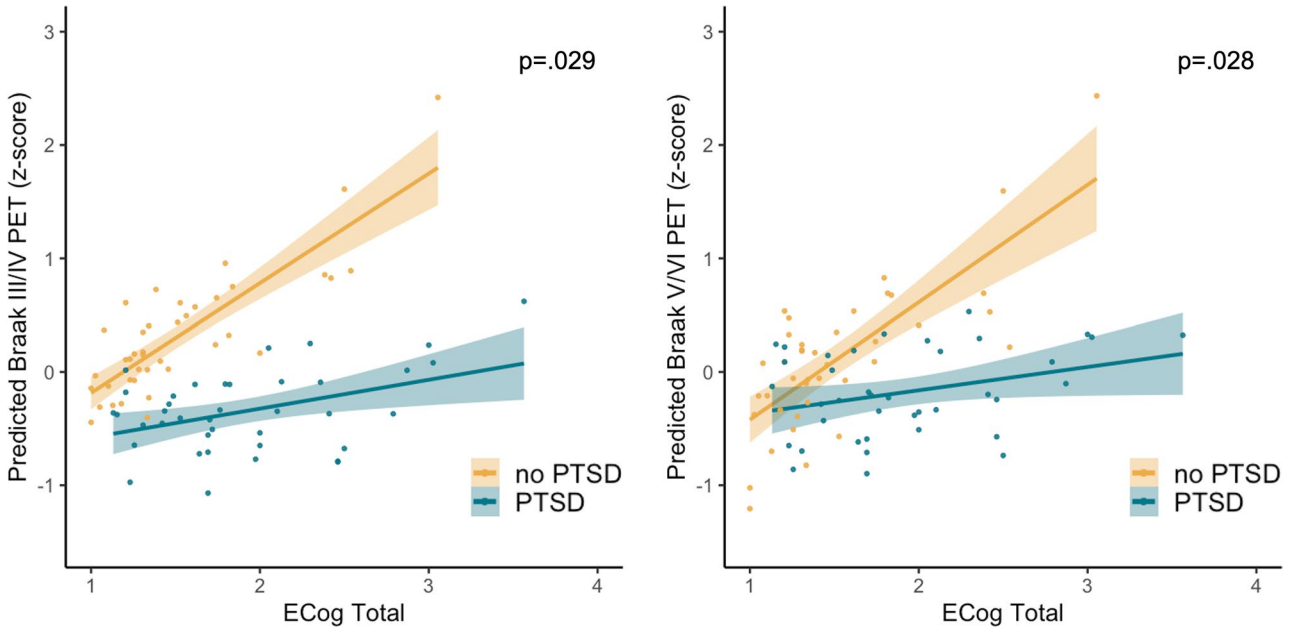

Figure 1. PTSD as the moderator between subjective cognitive decline (ECog) and tau PET levels. Predicted values of the fully-adjusted Braak III/IV (left) and V/VI (right) models.

and, to some extent, amyloid levels in older Veterans, several of these associations were moderated by PTSD status, such that there was a stronger positive association between SCD and tau in Veterans without PTSD relative to Veterans with PTSD. We also found a similar moderating effect of PTSD in the association between SCD and amyloid PET in the minimally adjusted model, potentially due to the frequently co-occurring nature of these two AD pathologies, especially at higher Braak stages (Pontecorvo et al., 2017). PTSD did not moderate the association between SCD and global cognition.

This study focused on tau PET stages given evidence that cognitive changes tend to be more strongly linked to tau accumulation than amyloid accumulation in prodromal and early stages of AD (Aschenbrenner et al., 2018; Weigand et al., 2021). Our primary hypothesis that PTSD moderates the association between SCD and tau PET levels was largely supported by our results. Specifically, Veterans with PTSD exhibited a weaker relationship between SCD and tau PET in Braak stages III/IV and V/VI (and in Braak I sensitivity analyses) compared to those without PTSD. This moderating effect remained significant even after adjusting for covariates such as APOE ε4 carrier status, race, ethnicity, and TBI severity. These findings suggest that the presence of PTSD may alter the relationship between SCD and AD-related tau pathology. Our study did not find a significant moderating effect of PTSD on the association between SCD and tau PET in Braak stage I when all participants were included; however, there was a significant moderating effect of PTSD for Braak I in the sensitivity analyses that excluded participants in which their baseline visit and tau PET scan were ≥24 months apart. Despite the smaller sample size in the sensitivity analysis ($n = 50$), it is possible that there was less error due to the shorter time interval between the baseline assessment (for ECog and PTSD variables) and the tau PET scan. This finding suggests that PTSD may moderate the association between SCD and very early tau accumulation.

Within DoD-ADNI, there are some inconsistent findings related to PTSD and tau and amyloid deposition. Prior work within DoD-ADNI shows that PTSD is not associated with elevated tau deposition or higher rates of amyloid positivity status (Andrews et al., 2021; Weiner et al., 2023). Within the subset of participants included in our study and when examining tau burden using approximate Braak staging, we found that, relative to Veterans with PTSD, those without PTSD showed higher levels of tau, especially in Braak III/IV. This was unexpected given previously null findings reported by Weiner et al. (2023), but the different way of examining regional tau PET in this study (Braak stages vs. metatemporal region), slightly lower age of Veterans with PTSD in this sample, and the possibility that older Veterans with both PTSD and high AD biomarkers were less likely to enroll/be eligible for DoD-ADNI may account for some of the differences. Our study also focused on examining differences in Veterans with and without PTSD only, whereas prior work used a 4-group design of controls, PTSD only, TBI only, and PTSD + TBI, making the group sizes quite small. It is possible that the participants without PTSD and with the highest tau values are driving the stronger associations of SCD and tau observed in this study; however, PTSD status was included in the model to adjust for differences by PTSD status. Notably, our study did not focus on the tau comparisons in Veterans with and without PTSD, but rather, whether the associations of subjective cognition with tau and amyloid deposition were impacted by PTSD status, which to our knowledge, has not yet been investigated.

The moderating impact of PTSD in this study highlights the importance of considering additional factors that may be contributing to the weaker associations in Veterans with PTSD. Factors such as specific PTSD symptoms like hyperarousal/concentration difficulties, sleep quality, substance use, metabolic and vascular risk, inflammation, and, potentially cognitive reserve may be more prominent contributors to SCD in older Veterans with PTSD relative to AD pathology (Andrews et al., 2021; Beristianos et al., 2016; Elias et al., 2021; Green et al., 2016; Lohr et al., 2015; Samuelson et al., 2006). While it may appear as though Veterans with PTSD are less accurate in their self-evaluation of cognition (i.e. 'over-reporting') based on the PET results, it is important to consider these other factors as potentially driving the SCD reported in those with PTSD. Specifically, it is possible that these *non-AD* factors that are often associated with or are co-occurring in older Veterans with PTSD are directly

impacting cognitive performance, which could explain why we did not find a moderating effect of PTSD status on the association between SCD and global cognitive performance. In the current study, there was a pattern such that Veterans with PTSD had higher pulse pressure, a marker of vascular risk thought to be a proxy for arterial stiffening (Nation et al., 2015). While pulse pressure was included as a covariate in the models, future work should investigate whether there is a stronger association between cognition and cerebrovascular disease in older Veterans with PTSD than in those without PTSD. This possibility would be consistent with prior work demonstrating diffusion tensor imaging (DTI) associations with cognition in PTSD and moderate-to-severe TBI groups within DoD-ADNI (Mohamed et al., 2021) as well as myelin changes in Veterans with PTSD, but not mild TBI (Jak et al., 2020).

While this is one of the largest samples of Veterans with tau PET imaging, we did not split the sample into four combinations of PTSD/TBI groups due to the small cell sizes. It is worth examining the combined impact of PTSD and TBI in moderating the associations of subjective and objective cognition with AD and other neurodegeneration biomarkers in the future. Another key next step is to examine PTSD as a moderator of the association between *objective* cognition (including specific cognitive domains) and AD biomarkers This study is also limited by the cross-sectional design and significant underrepresentation of women Veterans, in addition to limited diversity of race/ethnicity and high mean educational attainment in this sample (~15 years). Given the known sex-differences in AD risk and role of sex on associations between tau and cognition (Banks et al., 2021), future work needs to examine these associations within women. Regarding the PET scans, given this is a multisite study spanning many years, despite standardized protocols, slight differences in scanners may have introduced some degree of error. Further, while tau PET generally performs well in staging AD using Braak stages regions of interest, the use of Braak regions assumes that tau is distributed in a typical temporal-spatial pattern, so it may be limited in its utility for participants that may have atypical tau distribution (Macedo et al., 2023).

The current study highlights the importance of a nuanced workup for older Veterans with PTSD and/or who have subjective cognitive concerns. While older Veterans with PTSD may be less likely to have their subjective cognitive concern be due to AD pathology, some Veterans will have both AD pathology and PTSD and/or other health factors and neuropathology that are contributing to their report of SCD. Therefore, these cognitive concerns that may bring Veterans into the clinic should be properly worked up and given full consideration, as well as a thorough evaluation of non-pathologic factors that may be contributing to these legitimate subjective cognitive difficulties. Given the potential impact that PTSD and the distress of feeling like one's cognition is not as good as it was previously can have on someone's quality of life (Hill et al., 2017; Roehr et al., 2017; Zatzick et al., 1997), it is critical for Veterans to have access to comprehensive assessments that integrate mental health, neuropsychological, and biomarker information so that the contributing features of cognitive and functional difficulties may be better understood, and a personalized and targeted intervention plan may be implemented as early as possible.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

This work was supported by the U.S. Department of Veterans Affairs Clinical Sciences Research and Development Service (1IK2CX001865, 1I01CX001842, IK2CX001952), NIH/NIA grants (RF1AG082726, P30 AG062429, R03 AG070435, R01 AG063782), and the Alzheimer's Association (AARG-22-723000). Data collection and sharing for this project was funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI) (National Institutes of Health Grant U01 AG024904) and DOD ADNI (Department of Defense award number W81XWH-12-2-0012). 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; BioClinica, Inc.; Biogen Idec Inc.; Bristol-Myers Squibb Company; Eisai Inc.; Elan Pharmaceuticals, Inc.; Eli Lilly and Company; F. Hoffmann-La Roche Ltd and its affiliated company Genentech, Inc.; GE Healthcare; Innogenetics, N.V.; 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; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Piramal Imaging; Servier; Synarc Inc.; and Takeda Pharmaceutical Company. The Canadian Institutes of 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 Neuro Imaging at the University of Southern California. This research was also supported by NIH grants P30 AG010129 and K01 AG030514.

Data availability statement

The data supporting the findings of this study are openly available in loni repository for DoD-ADNI at https://ida.loni.usc.edu/.

References

Amariglio, R. E., Becker, J. A., Carmasin, J., Wadsworth, L. P., Lorius, N., Sullivan, C., Maye, J. E., Gidicsin, C., Pepin, L. C., Sperling, R. A., Johnson, K. A., & Rentz, D. M. (2012). Subjective cognitive complaints and amyloid burden in cognitively normal older individuals. *Neuropsychologia*, *50*(12), 2880–2886. https://doi.org/10.1016/j.neuropsychologia.2012.08.011

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed).

Andrews, M., Ross, R., Malhotra, A., Ancoli-Israel, S., Brewer, J. B., & Banks, S. J, Initiative, for the A. D. N. (2021). Sleep and Tau pathology in Vietnam war veterans with preclinical and prodromal Alzheimer's disease. *Journal of Alzheimer's Disease Reports*, *5*(1), 41–48. https://doi.org/10.3233/ADR-200245

Aschenbrenner, A. J., Gordon, B. A., Benzinger, T. L. S., Morris, J. C., & Hassenstab, J. J. (2018). Influence of tau PET, amyloid PET, and hippocampal volume on cognition in Alzheimer disease. *Neurology*, *91*(9), e859–e866. https://doi.org/10.1212/WNL.0000000000006075

Baker, S. L., Maass, A., & Jagust, W. J. (2017). Considerations and code for partial volume correcting [18F]-AV-1451 tau PET data. *Data in Brief*, *15*, 648–657. https://doi.org/10.1016/j.dib.2017.10.024

Banks, S. J., Andrews, M. J., Digma, L., Madsen, J., Reas, E. T., Caldwell, J. Z. K., McEvoy, L. K., Fan, C. C., Dale, A. M., & Brewer, J. B. (2021). Sex differences in Alzheimer's disease: Do differences in tau explain the verbal memory gap? *Neurobiology of Aging*, *107*, 70–77. https://doi.org/10.1016/j.neurobiolaging.2021.05.013

Beristianos, M. H., Yaffe, K., Cohen, B., & Byers, A. L. (2016). PTSD and risk of incident cardiovascular disease in aging veterans. *The American Journal of Geriatric Psychiatry: Official Journal of the American Association for Geriatric Psychiatry*, *24*(3), 192–200. https://doi.org/10.1016/j.jagp.2014.12.003

Braak, H., & Braak, E. (1991). Neuropathological stageing of Alzheimer-related changes. *Acta Neuropathologica*, *82*(4), 239–259. https://doi.org/10.1007/BF00308809

Buckley, R. F., Hanseeuw, B., Schultz, A. P., Vannini, P., Aghjayan, S. L., Properzi, M. J., Jackson, J. D., Mormino, E. C., Rentz, D. M., Sperling, R. A., Johnson, K. A., & Amariglio, R. E. (2017). Region-specific association of subjective cognitive decline with tauopathy independent of global β-amyloid burden. *JAMA Neurology*, *74*(12), 1455–1463. https://doi.org/10.1001/jamaneurol.2017.2216

Buckley, R. F., Sikkes, S., Villemagne, V. L., Mormino, E. C., Rabin, J. S., Burnham, S., Papp, K. V., Doré, V., Masters, C. L., Properzi, M. J., Schultz, A. P., Johnson, K. A., Rentz, D. M., Sperling, R. A., & Amariglio, R. E. (2019). Using subjective cognitive decline to identify high global amyloid in community-based samples: A cross-cohort study. *Alzheimer's & Dementia (Amsterdam, Netherlands)*, *11*(C), 670–678. https://doi.org/10.1016/j.dadm.2019.08.004

Chapman, S., Rentería, M. A., Dworkin, J. D., Garriga, S. M., Barker, M. S., Avila-Rieger, J., Gonzalez, C., Joyce, J. L., Vonk, J. M. J., Soto, E., Manly, J. J., Brickman, A. M., Mayeux, R. P., & Cosentino, S. A. (2023). Association of subjective cognitive decline with progression to dementia in a cognitively unimpaired multiracial community sample. *Neurology*, *100*(10), e1020–e1027. https://doi.org/10.1212/WNL.0000000000201658

Department of Veterans Affairs and Department of Defense. (2021). Clinical practice guideline for the management and rehabilitation of post-acute mild traumatic brain injury. https://www.google.com/url?q=https://www.healthquality.va.gov/guidelines/rehab/mtbi/&sa=D&source=docs&ust=1666311803014387&usg=AOvVaw1lG7gP5RR14aoPJUfrntT7

Elias, A., Rowe, C., & Hopwood, M. (2021). Risk of dementia in posttraumatic stress disorder. *Journal of Geriatric Psychiatry and Neurology*, *34*(6), 555–564. https://doi.org/10.1177/0891988720957088

Farias, S. T., Mungas, D., Reed, B. R., Cahn-Weiner, D., Jagust, W., Baynes, K., & DeCarli, C. (2008). The measurement of everyday cognition (ECog): Scale development and psychometric properties. *Neuropsychology*, *22*(4), 531–544. https://doi.org/10.1037/0894-4105.22.4.531

Gordon, B. A., Blazey, T. M., Christensen, J., Dincer, A., Flores, S., Keefe, S., Chen, C., Su, Y., McDade, E. M., Wang, G., Li, Y., Hassenstab, J., Aschenbrenner, A., Hornbeck, R., Jack, C. R., Ances, B. M., Berman, S. B., Brosch, J. R., Galasko, D., … Benzinger, T. L. S. (2019). Tau PET in autosomal dominant Alzheimer's disease: Relationship with cognition, dementia and other biomarkers. *Brain: A Journal of Neurology*, *142*(4), 1063–1076. https://doi.org/10.1093/brain/awz019

Green, E., Fairchild, J. K., Kinoshita, L. M., Noda, A., & Yesavage, J. (2016). Effects of posttraumatic stress disorder and metabolic syndrome on cognitive aging in veterans. *The Gerontologist*, *56*(1), 72–81. https://doi.org/10.1093/geront/gnv040

Günak, M. M., Billings, J., Carratu, E., Marchant, N. L., Favarato, G., & Orgeta, V. (2020). Post-traumatic stress disorder as a risk factor for dementia: Systematic review and meta-analysis. *The British Journal of Psychiatry: The Journal of Mental Science*, *217*(5), 600–608. https://doi.org/10.1192/bjp.2020.150

Hill, N. L., McDermott, C., Mogle, J., Munoz, E., DePasquale, N., Wion, R., & Whitaker, E. (2017). Subjective cognitive impairment and quality of life: A systematic review. *International Psychogeriatrics*, *29*(12), 1965–1977. https://doi.org/10.1017/S1041610217001636

Jak, A. J., Jurick, S., Hoffman, S., Evangelista, N. D., Deford, N., Keller, A., Merritt, V. C., Sanderson-Cimino, M., Sorg, S., Delano-Wood, L., & Bangen, K. J. (2020). PTSD, but not history of mTBI, is associated with altered myelin in combat-exposed Iraq and Afghanistan Veterans. *The Clinical Neuropsychologist*, *34*(6), 1070–1087. https://doi.org/10.1080/13854046.2020.1730975

Jessen, F., Amariglio, R. E., van Boxtel, M., Breteler, M., Ceccaldi, M., Chételat, G., Dubois, B., Dufouil, C., Ellis, K. A., van der Flier, W. M., Glodzik, L., van Harten, A. C., de Leon, M. J., McHugh, P., Mielke, M. M., Molinuevo, J. L., Mosconi, L., Osorio, R. S., Perrotin, A., … Wagner, M. (2014). A conceptual framework for research on subjective cognitive decline in preclinical Alzheimer's disease. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*, *10*(6), 844–852. https://doi.org/10.1016/j.jalz.2014.01.001

Kessler, R. C., Berglund, P., Demler, O., Jin, R., Merikangas, K. R., & Walters, E. E. (2005). Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the national comorbidity survey replication. *Archives of General Psychiatry*, *62*(6), 593–602. https://doi.org/10.1001/archpsyc.62.6.593

Kulka, R. A., Schlenger, W. E., Fairbank, J. A., Hough, R. L., Jordan, B. K., Marmar, C. R., & Weiss, D. S. (1990). *Trauma and the Vietnam war generation: Report of findings from the National Vietnam Veterans Readjustment Study* (pp. xxix, 322). Brunner/Mazel.

Kuring, J. K., Mathias, J. L., & Ward, L. (2020). Risk of dementia in persons who have previously experienced clinically-significant depression, anxiety, or PTSD: A systematic review and meta-analysis. *Journal of Affective Disorders*, *274*, 247–261. https://doi.org/10.1016/j.jad.2020.05.020

Landau, S., Ward, T. J., Jagust, W. J. (2021). *Flortaucipir (AV-1451) processing methods*. http://adni.loni.usc.edu/

Lohr, J. B., Palmer, B. W., Eidt, C. A., Aailaboyina, S., Mausbach, B. T., Wolkowitz, O. M., Thorp, S. R., & Jeste, D. V. (2015). Is post-traumatic stress disorder associated with premature senescence? A review of the literature. *The American Journal of Geriatric Psychiatry: Official Journal of the American Association for Geriatric Psychiatry*, *23*(7), 709–725. https://doi.org/10.1016/j.jagp.2015.04.001

Macedo, A. C., Tissot, C., Therriault, J., Servaes, S., Wang, Y.-T., Fernandez-Arias, J., Rahmouni, N., Lussier, F. Z., Vermeiren, M., Bezgin, G., Vitali, P., Ng, K. P., Zimmer, E. R., Guiot, M.-C., Pascoal, T. A., Gauthier, S., & Rosa-Neto, P. (2023). The use of tau PET to stage Alzheimer disease according to the Braak staging framework. *Journal of Nuclear Medicine: Official Publication, Society of Nuclear Medicine*, *64*(8), 1171–1178. https://doi.org/10.2967/jnumed.122.265200

Mattson, E. K., Nelson, N. W., Sponheim, S. R., & Disner, S. G. (2019). The impact of PTSD and mTBI on the relationship between subjective and objective cognitive deficits in combat-exposed veterans. *Neuropsychology*, *33*(7), 913–921. https://doi.org/10.1037/neu0000560

Merritt, V. C., Jurick, S. M., Crocker, L. D., Hoffman, S. N., Keller, A. V., DeFord, N., & Jak, A. J. (2019). Evaluation of objective and subjective clinical outcomes in combat veterans with and without mild TBI and PTSD: A four-group design. *Journal of Clinical and Experimental Neuropsychology*, *41*(7), 665–679. https://doi.org/10.1080/13803395.2019.1610161

Mohamed, A. Z., Cumming, P., & Nasrallah, F. A. (2021). White matter alterations are associated with cognitive dysfunction decades after moderate-to-severe traumatic brain injury and/or posttraumatic stress disorder. *Biological Psychiatry. Cognitive Neuroscience and Neuroimaging*, *6*(11), 1100–1109. https://doi.org/10.1016/j.bpsc.2021.04.014

Morris, J. C. (1993). The clinical dementia rating (CDR): Current version and scoring rules. *Neurology*, *43*(11), 2412–2414. https://doi.org/10.1212/wnl.43.11.2412-a

Nation, D. A., Edmonds, E. C., Bangen, K. J., Delano-Wood, L., Scanlon, B. K., Han, S. D., Edland, S. D., Salmon, D. P., Galasko, D. R., & Bondi, M. W. (2015). Pulse pressure in relation to tau-mediated neurodegeneration, cerebral amyloidosis, and progression to dementia in very old adults. *JAMA Neurology*, *72*(5), 546–553. https://doi.org/10.1001/jamaneurol.2014.4477

Ossenkoppele, R., Schonhaut, D. R., Schöll, M., Lockhart, S. N., Ayakta, N., Baker, S. L., O'Neil, J. P., Janabi, M., Lazaris, A., Cantwell, A., Vogel, J., Santos, M., Miller, Z. A., Bettcher, B. M., Vossel, K. A., Kramer, J. H., Gorno-Tempini, M. L., Miller, B. L., Jagust, W. J., & Rabinovici, G. D. (2016). Tau PET patterns mirror clinical and neuroanatomical variability in Alzheimer's disease. *Brain: A Journal of Neurology*, *139*(Pt 5), 1551–1567. https://doi.org/10.1093/brain/aww027

Papp, K. V., Buckley, R., Mormino, E., Maruff, P., Villemagne, V. L., Masters, C. L., Johnson, K. A., Rentz, D. M., Sperling, R. A., & Amariglio, R. E. (2020). Clinical meaningfulness of subtle cognitive decline on longitudinal testing in preclinical AD. *Alzheimer's & Dementia* , *16*, 552–560. https://doi.org/10.1016/j.jalz.2019.09.074

Pontecorvo, M. J., Devous, M. D., Sr, Navitsky, M., Lu, M., Salloway, S., Schaerf, F. W., Jennings, D., Arora, A. K., McGeehan, A., Lim, N. C., Xiong, H., Joshi, A. D., Siderowf, A., & Mintun, M. A. (2017). Relationships between flortaucipir PET tau binding and amyloid burden, clinical diagnosis, age and cognition. *Brain: A Journal of Neurology*, *140*(3), 748–763. https://doi.org/10.1093/brain/aww334

Prieto, S., Moody, J. N., Valerio, K. E., & Hayes, J. P. (2022). Posttraumatic stress disorder symptom severity is associated with reduced Montreal Cognitive Assessment scores in a sample of Vietnam War Veterans. *Journal of Traumatic Stress*, *35*(4), 1282–1290. https://doi.org/10.1002/jts.22830

Rantins, P., Ly, M., Clark, A. L., Weigand, A. J., Alshaheri Durazo, A., Merritt, V. C., Bangen, K. J., & Thomas, K. R. (2024). Research letter: TBI severity moderates the association between subjective and objective attention in older veterans. *The Journal of Head Trauma Rehabilitation*, *39*(3), 239–246. https://doi.org/10.1097/HTR.0000000000000897

Roehr, S., Luck, T., Pabst, A., Bickel, H., König, H.-H., Lühmann, D., Fuchs, A., Wolfsgruber, S., Wiese, B., Weyerer, S., Mösch, E., Brettschneider, C.,

Mallon, T., Pentzek, M., Wagner, M., Mamone, S., Werle, J., Scherer, M., Maier, W., Jessen, F., … Riedel-Heller, S. G. (2017). Subjective cognitive decline is longitudinally associated with lower health-related quality of life. *International Psychogeriatrics*, *29*(12), 1939–1950. https://doi.org/10.1017/S1041610217001399

Samuelson, K. W., Neylan, T. C., Metzler, T. J., Lenoci, M., Rothlind, J., Henn-Haase, C., Choucroun, G., Weiner, M. W., & Marmar, C. R. (2006). Neuropsychological functioning in posttraumatic stress disorder and alcohol abuse. *Neuropsychology*, *20*(6), 716–726. https://doi.org/10.1037/0894-4105.20.6.716

Schuitevoerder, S., Rosen, J. W., Twamley, E. W., Ayers, C. R., Sones, H., Lohr, J. B., Goetter, E. M., Fonzo, G. A., Holloway, K. J., & Thorp, S. R. (2013). A meta-analysis of cognitive functioning in older adults with PTSD. *Journal of Anxiety Disorders*, *27*(6), 550–558. https://doi.org/10.1016/j.janxdis.2013.01.001

Sheikh, J. I., & Yesavage, J. A. (1986). Geriatric depression scale (GDS): Recent evidence and development of a shorter version. *Clinical Gerontologist: The Journal of Aging and Mental Health*, *5*, 165–173. https://doi.org/10.1300/J018v05n01_09

Song, H., Sieurin, J., Wirdefeldt, K., Pedersen, N. L., Almqvist, C., Larsson, H., Valdimarsdóttir, U. A., & Fang, F. (2020). Association of stress-related disorders with subsequent neurodegenerative diseases. *JAMA Neurology*, *77*(6), 700–709. https://doi.org/10.1001/jamaneurol.2020.0117

Thomas, K. R., Weigand, A. J., Edwards, L. C., Edmonds, E. C., Bangen, K. J., Ortiz, G., Walker, K. S., & Bondi, M. W. (2022). Tau levels are higher in objective subtle cognitive decline but not subjective memory complaint. *Alzheimer's Research & Therapy*, *14*(1), 114. https://doi.org/10.1186/s13195-022-01060-1

Vasterling, J. J., Duke, L. M., Brailey, K., Constans, J. I., Allain, A. N., Jr., & Sutker, P. B. (2002). Attention, learning, and memory performances and intellectual resources in Vietnam veterans: PTSD and no disorder comparisons. *Neuropsychology*, *16*(1), 5–14. https://doi.org/10.1037/0894-4105.16.1.5

Weigand, A. J., Bangen, K. J., Thomas, K. R., Delano-Wood, L., Gilbert, P. E., Brickman, A. M., & Bondi, M. W. (2020). Is tau in the absence of amyloid on the Alzheimer's continuum?: A study of discordant PET positivity. *Brain Communications*, *2*(1), fcz046. https://doi.org/10.1093/braincomms/fcz046

Weigand, A. J., Thomas, K. R., Bangen, K. J., Eglit, G. M. L., Delano-Wood, L., Gilbert, P. E., Brickman, A. M., & Bondi, M. W. (2021). APOE interacts with tau PET to influence memory independently of amyloid PET in older adults without dementia. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*, *17*(1), 61–69. https://doi.org/10.1002/alz.12173

Weiner, M. W., Harvey, D., Landau, S. M., Veitch, D. P., Neylan, T. C., Grafman, J. H., Aisen, P. S., Petersen, R. C., Jack, C. R., Jr, Tosun, D., Shaw, L. M., Trojanowski, J. Q., Saykin, A. J., Hayes, J., & De Carli, C. (2023). Traumatic brain injury and post-traumatic stress disorder are not associated with Alzheimer's disease pathology measured with biomarkers. *Alzheimer's & Dementia*, *19*(3), 884–895. https://doi.org/10.1002/alz.12712

Weiner, M. W., Veitch, D. P., Hayes, J., Neylan, T., Grafman, J., Aisen, P. S., Petersen, R. C., Jack, C., Jagust, W., Trojanowski, J. Q., Shaw, L. M., Saykin, A. J., Green, R. C., Harvey, D., Toga, A. W., Friedl, K. E., Pacifico, A., Sheline, Y., … Yaffe, K. (2014). Effects of traumatic brain injury and posttraumatic stress disorder on Alzheimer's disease in veterans, using the Alzheimer's Disease Neuroimaging Initiative. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*, *10*(3 Suppl), S226–S235. https://doi.org/10.1016/j.jalz.2014.04.005

Yaffe, K., Vittinghoff, E., Lindquist, K., Barnes, D., Covinsky, K. E., Neylan, T., Kluse, M., & Marmar, C. (2010). Posttraumatic stress disorder and risk of dementia among US veterans. *Archives of General Psychiatry*, *67*(6), 608–613. https://doi.org/10.1001/archgenpsychiatry.2010.61

Zatzick, D. F., Marmar, C. R., Weiss, D. S., Browner, W. S., Metzler, T. J., Golding, J. M., Stewart, A., Schlenger, W. E., & Wells, K. B. (1997). Posttraumatic stress disorder and functioning and quality of life outcomes in a nationally representative sample of male Vietnam veterans. *The American Journal of Psychiatry*, *154*(12), 1690–1695. https://doi.org/10.1176/ajp.154.12.1690