Journal of Alzheimer's Disease Reports 6 (2022) 49–56
DOI 10.3233/ADR-210048
IOS Press

Research Report

Blood-Based Biomarkers for Alzheimer's Disease in Older Adults with Posttraumatic Stress Disorder

Nicolas Cimino[a], Min Suk Kang[b], Lawrence S. Honig[b] and Bret R. Rutherford[a,b,*]
[a]*New York State Psychiatric Institute, New York, NY, USA*
[b]*Columbia University Vagelos College of Physicians and Surgeons, New York, NY, USA*

Received 6 October 2022
Accepted 4 January 2022
Pre-press 25 January 2022
Published 2 February 2022

Abstract.
Background: Posttraumatic stress disorder (PTSD) is associated with cognitive decline and risk for dementia, but the neuropathology involved is unclear.
Objective: The aim of this study was to determine whether PTSD is associated with increased levels of Alzheimer's disease (AD) blood-based biomarkers.
Methods: Individuals aged 50 years and older with PTSD were compared to trauma-exposed healthy controls (TEHCs) at baseline on serum measures of amyloid-β (Aβ) 42 and 40 levels, the $A\beta_{42}/A\beta_{40}$ ratio, and total tau. Serum was analyzed using ultrasensitive Simoa Human Neurology 3-Plex A assay (N3PA). Linear regressions modeling each AD biomarker as a function of group were used to investigate between-group differences, controlling for age, sex, and educational attainment (years).
Results: TEHC participants ($N = 26$) were 53.8% male with mean age 66.8 ± 10.7, whereas PTSD participants ($N = 44$) were 47.7% male and aged 62.5 ± 9.1 years. No between-group differences were noted on demographic characteristics or cognitive performance measured with the NIH Toolbox Cognition Battery. There were no significant between-group differences in serum $A\beta_{40}$ (TEHC 105.8 ± 51.6 versus PTSD 93.2 ± 56.1, $p = 0.46$), $A\beta_{42}$ (TEHC 8.1 ± 4.6 versus PTSD 7.8 ± 4.6, $p = 0.63$), $A\beta_{42}/A\beta_{40}$ (TEHC 0.08 ± 0.03 versus PTSD 0.09 ± 0.03, $p = 0.27$), or total tau (TEHC 0.5 ± 0.3 versus PTSD 0.5 ± 0.4, $p = 0.77$). Likewise, there were no significant interaction effects of amyloid or tau serum concentrations and PTSD group status on cognitive functioning.
Conclusion: Findings from cognitive assessments and serum analyses do not support PTSD-induced neurodegeneration of the Alzheimer's type as a pathway linking PTSD to increased incidence of dementia in older adults.

Keywords: Alzheimer's disease, dementia, posttraumatic stress disorder, trauma

INTRODUCTION

Posttraumatic stress disorder (PTSD) affects nearly 7% of American adults [1] and is associated with elevated rates of disability [2], comorbid medical and psychiatric disorders [3], and suicide [4, 5]. PTSD among older adults has been increasing in prevalence [6, 7], a pattern which is anticipated to accelerate as the population ages and Veterans from recent conflicts age [8]. Most older adults with PTSD suffer from chronic symptoms, which is associated with at least one functional role disability in nearly

*Correspondence to: Bret R. Rutherford, MD, New York State Psychiatric Institute, 1051 Riverside Dr, Box 98, New York, NY 10032, USA. Tel.: +1 646 774 8660;
E-mail: brr8@cumc.columbia.edu.

80% of cases [6]. Contributing to the high disability rates observed among older adults with PTSD, cognitive performance decrements across domains has been observed in individuals with PTSD compared to trauma-exposed older adults without PTSD and healthy controls [9].

Notably, midlife and older patients with PTSD exhibit increased risk for cognitive decline and diagnosis with dementia compared to age-matched peers without PTSD [10, 11]. A recent cohort study including over 10,000 Veterans found that the odds of dementia diagnosis in PTSD patients over 10 years follow-up were two times as high as those without PTSD [12]. Significantly increased incidence of dementia has been replicated in a larger study of nearly 200,000 Veterans, where the cumulative incidence of dementia over 7 years follow-up was 10.6% for those with PTSD compared to 6.6% for Veterans without PTSD [13]. Both of these analyses adjusted for the presence of combat-related trauma, greater health-service use, comorbid medical and psychiatric disorders, and substance use, meaning that PTSD confers an independent risk for dementia over and above the multitude of comorbidities with which it is frequently associated. Adding to this evidence, studies of non-Veterans, including public service workers exposed to trauma during the September 11, 2001 attacks, have reported poorer subsequent cognitive functioning among World Trade Center responders compared to general population norms [14]. Longitudinal study of these individuals found that PTSD symptom severity was linked to increased risk of cognitive impairment over time [15].

Despite these strong epidemiologic links between PTSD and a clinical diagnosis of dementia, the neuropathology linking these conditions has yet to be elucidated. For example, it remains unclear whether the presence of PTSD is associated with increased amyloid-β (Aβ) plaque burden, which is a hallmark of Alzheimer's disease (AD) neuropathology. In the largest analysis to date, the Alzheimer's Disease Neuroimaging Initiative (ADNI) collected serial magnetic resonance imaging (MRI) and amyloid-imaging positron emission tomography (PET) scans combined with clinical and neuropsychological assessments to investigate the potential effect of PTSD on risk for progression to AD [16]. Initial analysis of these amyloid PET scans collected from ADNI indicated no effect of PTSD on amyloid burden and subsequent AD risk, though a voxel-based re-analysis revealed significantly greater amyloid accumulation in the frontal, occipital, and temporal lobes of PTSD participants with significant cognitive dysfunction compared to healthy controls [17]. Pilot work in World Trade Center responders with PTSD demonstrated a significantly lower plasma total Aβ concentration but, paradoxically, a trend toward increased $A\beta_{42}/A\beta_{40}$ compared to World Trade Center responders who did not have PTSD [18]. A larger follow-up study showed that $A\beta_{42}$ and total tau levels showed various associations with cognitive impairment, although since there was no control group, it remains unclear whether links between biomarkers and cognitive decline are greater among individuals with PTSD compared to the general population [19].

The strong associations between the presence of PTSD and subsequent cognitive decline, coupled with the as yet uncertain neuropathology linking these conditions, motivated us to investigate the association of PTSD with blood-based AD biomarkers in a well-matched and comprehensively characterized sample of older adults with PTSD and trauma-exposed healthy controls (TEHCs). Individuals aged 50 years and older meeting DSM5 criteria for PTSD of at least one year duration as well as TEHCs underwent psychiatric, cognitive, and physical functioning assessment. In addition, serum samples were analyzed for $A\beta_{42}$ and $A\beta_{40}$ levels as well as total tau level. We hypothesized that if AD pathology was responsible for cognitive changes, the $A\beta_{42}/A\beta_{40}$ ratio would be lower and total tau levels would be higher in PTSD participants compared to controls. Moreover, we expected that lower $A\beta_{42}/A\beta_{40}$ ratio and higher total tau levels would be significantly correlated with impaired episodic memory performance on the NIH Cognition Toolbox Battery.

MATERIALS AND METHODS

Participant selection

Participants for this study were recruited at Columbia University/New York State Psychiatric Institute (NYSPI) and the James J. Peters Veterans Affairs Medical Centre (JJP VAMC) of the Icahn School of Medicine at Mount Sinai (ISMMS). PTSD subjects were ≥ 50 years of age, of either sex, diagnosed with PTSD according to Diagnostic and Statistical Manual–5 (DSM-5) criteria [20] established using the Structured Clinical Interview for DSM-5 (SCID 5) [21], with a duration of at least one year, with a Posttraumatic Stress Disorder Checklist (PCL-5) score ≥ 33 and a Clinician-Administered

PTSD Scale for DSM-5 (CAPS-5) score ≥ 25. Subjects were excluded for 1) past or current diagnosis of traumatic brain injury, bipolar disorder, psychotic disorder, or dementia, 2) current or within the past 6 months severe Alcohol/Cannabis Use Disorder or any other Substance Use Disorder except Nicotine, 3) current treatment with mood stabilizers or antipsychotic medications, 4) Mini-Mental Status Examination (MMSE) score < 25, or 5) acute, unstable, or severe medical disorder.

The TEHC group comprised men and women aged ≥ 50 years old who were exposed to a PTSD Criterion A trauma. Controls were excluded if they had personal history of traumatic brain injury, current or past DSM-5 disorder, PTSD diagnosed in a first degree relative, current treatment with psychotherapy or psychotropic medications such as antidepressants, mood stabilizers, antipsychotic, or sedative/hypnotic medications, past or current diagnosis of dementia or MMSE < 25, HRSD > 7, or CAPS-5 ≥ 10.

Clinical study assessments

In addition to the above assessments, the type and time of trauma exposure in participants was assessed using the Life Events Checklist for DSM 5 (LEC-5). Psychiatric symptoms were measured with the Hamilton Anxiety Rating Scale (HARS), the 24-item Hamilton Rating Scale for Depression (HRSD), and the Inventory of Depressive Symptoms—Self Report (IDS-SR). The CAGE AID Questionnaire screened for alcohol and drug abuse, supplemented by the Drug Abuse Screen Test (DAST) and the Michigan Alcohol Screen Test (MAST).

The primary cognitive measure was the NIH Toolbox Cognition Battery, which is a brief, diverse, accessible, and psychometrically sound set of seven computerized instruments that measure six ability subdomains important for cognitive health. In addition, processing speed was further assessed using the Digit Symbol test from the WAIS-III and the Pattern and Letter Comparison tests [22], while motor speed and attention were assessed with the Trail Making Test Part A. Episodic memory functioning was evaluated using the Rey Auditory Verbal Learning Test.

Alzheimer's disease biomarker collection and analysis

In this study, only serum, not plasma, was available for analysis. Blood was drawn and centrifuged (1450 g, 16 min) at room temperature. Serum was aliquoted into polypropylene tubes and promptly stored at –80°C. Analytes were measured in coded tubes, blinded to identity, status, or characteristics. Serum was thawed, centrifuged, and immediately analyzed using the ultrasensitive multiplex Simoa Human Neurology 3-Plex A (N3PA) assay kit (Quanterix, Lexington, MA, USA), which is a digital immunoassay measuring three biomarkers: $A\beta_{42}$, $A\beta_{40}$, and total tau. This kit has been extensively used for plasma measurements of these analytes, but also has been used for serum measurements, with good performance for $A\beta_{42}$ and $A\beta_{40}$ although lesser performance for tau. Lower limits of quantifications for these three analytes are reported as 0.142, 0.675, and 0.142 pg/mL respectively, compared to the average levels in these samples of 7.9, 97.9, and 0.48 pg/mL respectively. We measured each sample in duplicate using two 25 μL aliquots (each diluted 1:4) on 96-well plates using the Quanterix SR-X platform; each assay plate contains 8 duplicate calibrators of different concentrations, and positive and negative controls. Average coefficients of variation for the serum duplicates for $A\beta_{42}$, $A\beta_{40}$, and tau levels in the serum samples reported here were 7.0%, 4.9%, and 15.9% respectively.

Statistical analysis

Descriptive statistics for the sample at baseline were computed and compared across groups using independent samples *t*-tests for continuous measures and chi-square tests for categorical variables.

The relationships between group status (PTSD versus TEHC) and the AD biomarker outcomes of interest ($A\beta_{42}$ and $A\beta_{40}$ levels, $A\beta_{42}/A\beta_{40}$, and total tau level) were examined using linear regressions. Separate regressions modeled each AD biomarker as a function of group. Control variables in all regressions were age, sex, and educational attainment (years). Lastly, we further explored the hypothesis that group status might not only influence AD biomarker levels, but also the relationship between biomarkers and cognitive measures. Separate linear regressions of each NIH Toolbox Cognition Battery domain score, as well as the total score, were therefore performed on group (PTSD versus TEHC), biomarkers ($A\beta_{42}$ and $A\beta_{40}$ levels, $A\beta_{42}/A\beta$, and total tau level), and variables for the interactions between group and each biomarker. We opted not to utilize a correction for multiple comparisons, as given the small sample size in this study, this type of correction would mask nearly all findings.

Table 1
Clinical and demographic characteristics for participants with posttraumatic stress disorder (PTSD) and trauma-exposed healthy controls (TEHC)

	PTSD ($n = 44$)		TEHC ($n = 26$)		Difference Between Groups		
Variables	n	Mean ± SD or %	n	Mean ± SD or %	t	df	p
Age	44	62.5 ± 9.1	26	66.82 ± 10.67	1.8	68	0.077
Sex					0.24	1	0.621
Male	21	47.73%	14	53.85%			
Female	23	52.27%	12	46.15%			
Race					5.86	4	0.21
Asian	1	2.27%	0	0.0%			
Black/African American	12	27.27%	12	46.15%			
More than one	1	2.27%	0	0.0%			
Other	5	11.36%	0	0.0%			
White	25	56.82%	14	53.85%			
Ethnicity					0.01	1	0.913
Not Hispanic	36	81.82%	21	80.77%			
Hispanic	8	18.18%	5	19.23%			
Education					7.06	4	0.133
High school	12	27.27%	3	11.54%			
Technical School	2	4.55%	2	7.69%			
Some College	7	15.91%	10	38.46%			
College graduate	13	29.55%	4	15.38%			
Graduate degree	10	22.73%	7	26.92%			
Education (y)	44	14.98 ± 2.55	24	14.75 ± 1.96	–0.38	66	0.71
Veteran					0.01	1	0.936
Yes	10	27.03%	6	26.09%			
No	27	72.97%	17	73.91%			
Substance Use					1.22	1	0.270
Yes	2	4.55%	0	0.0%			
No	42	95.45%	26	100.0%			
Cumulative Illness Rating Scale—Geriatric	44	4.68 ± 3.9	26	2.73 ± 2.54	–2.28	68	0.026
PTSD Checklist for DSM5	44	41.8 ± 13.4	26	8.85 ± 9.12	–11.09	68	< 0.001
Clinician Administered PTSD Scale for DSM5	44	32.98 ± 7.41	26	2.88 ± 3.14	–19.64	68	< 0.001
Time Since Trauma (y)	31	34.52 ± 18	19	36.84 ± 23.35	0.39	48	0.695
SCID Depression					34.83	1	< 0.001
Yes	32	72.72%	0	0.0%			
No	12	27.27%	26	100.0%			
Hamilton Anxiety Rating Scale	44	18.25 ± 8.73	26	2.88 ± 2.75	–8.7	68	< 0.001
Hamilton Rating Scale for Depression	44	20.05 ± 7.88	26	2.31 ± 1.95	–11.25	68	< 0.001
Inventory for Depressive Symptomatology—SR	43	31.81 ± 12.77	25	8.52 ± 6.15	–8.54	66	< 0.001
Mini-Mental State Exam	44	28.68 ± 1.25	26	29 ± 0.98	1.11	68	0.272

RESULTS

Participant characteristics

TEHC participants ($N = 26$) were 53.8% male with mean age 66.8 ± 10.7, whereas PTSD participants ($N = 44$) were 47.7% male and aged 62.5 ± 9.1 years. The two groups did not differ significantly across demographic characteristics (see Table 1), being comparable on mean age, sex, race, ethnicity, education, trauma type, trauma severity, time since trauma, substance use, and veteran status. Roughly one quarter of PTSD subjects were receiving treatment with antidepressants and/or psychotherapy, and nearly three out of every four individuals with PTSD were also diagnosed with Major Depressive Disorder. As expected, PTSD participants scored significantly higher on symptom measures (CAPS-5 and HRSD-24) compared to TEHC subjects.

As shown in Table 2, the PTSD and TEHC groups did not significantly differ on the NIH Toolbox total score, nor on any one of its constituent subscales. The two groups likewise did not differ on supplementary measures of processing speed (Digit Symbol, Pattern and Letter comparison tests, Trail Making Test Part A) or on episodic memory (Selective Reminding Test immediate and delayed).

Table 2
Cognitive and physical functioning measures for participants with posttraumatic stress disorder (PTSD) and trauma-exposed healthy controls (TEHC)

	PTSD ($n=44$)		TEHC ($n=26$)		Difference Between Groups		
Variables	n	Mean ± SD or %	n	Mean ± SD or %	t	df	p
Trail Making Test Part A	44	44.2 ± 20.23	26	38.38 ± 10.36	–1.36	68	0.178
Digit Symbol	44	44.43 ± 11.09	26	47.62 ± 12.67	1.1	68	0.275
SRT Immediate Recall	44	52.25 ± 8.64	26	50.35 ± 8.89	–0.88	68	0.381
SRT Delayed Recall	44	8.18 ± 2.37	26	7.96 ± 2.54	–0.37	68	0.716
NIH Toolbox Cognition Batter							
Picture Vocabulary	43	99.28 ± 37.95	26	107.92 ± 24.22	1.04	67	0.303
Oral Reading Recognition	43	98.53 ± 36.81	26	106.54 ± 23.2	0.99	67	0.324
List Sorting Working Memory	43	97.23 ± 8.83	26	94.27 ± 9.62	–1.31	67	0.196
Pattern Comparison	43	82.86 ± 15.85	26	86.04 ± 14.06	0.84	67	0.403
Picture Sequence Memory	43	97.79 ± 16.9	26	94.42 ± 11.41	–0.9	67	0.372
Flanker Inhibitory Control	43	89 ± 10.7	26	92.23 ± 6.81	1.38	67	0.173
Dimensional Card Sort	43	95.95 ± 9.68	26	98.85 ± 7.13	1.32	67	0.191
Total Composite Score	43	99.91 ± 10.66	26	100 ± 8.49	0.04	67	0.97
Measure of Everyday Cognition							
Memory	43	16.49 ± 7.77	25	11.52 ± 3.58	–3.01	66	0.004
Planning	43	8 ± 4.11	25	5.72 ± 2.51	–2.51	66	0.015
Organization	43	12.07 ± 6.39	25	7.72 ± 3.88	–3.08	66	0.003
Visual-spatial	43	9.67 ± 5.76	25	8.04 ± 2.41	–1.35	66	0.182
Language	43	14.91 ± 7.75	25	11.68 ± 3.54	–1.96	66	0.054
Divided Attention	43	8.42 ± 4.24	25	4.92 ± 1.93	–3.89	66	<0.001
Total	43	69.56 ± 32.71	25	49.6 ± 15.71	–2.86	66	0.006
WHODAS	42	79.88 ± 25.32	26	43.19 ± 8.78	–7.11	66	<0.001
Gait speed	44	1.1 ± 0.25	26	1.26 ± 0.25	2.48	68	0.016
Grip Strength	44	26.3 ± 15.35	26	29.07 ± 13.65	0.76	68	0.45
Pittsburgh Fatigability Scale	43	39.86 ± 23.05	25	14.64 ± 15.72	–4.85	66	<0.001
Mental fatigability subscale	43	18.58 ± 12.2	25	4.48 ± 7.44	–5.23	66	<0.001
Physical fatigability subscale	43	21.28 ± 11.87	25	10.16 ± 9.24	–4.02	66	<0.001
Short Physical Performance Battery	44	9.84 ± 1.83	26	10.88 ± 1.21	2.59	68	0.012

Table 3
Alzheimer's disease (AD) biomarker measures for participants with posttraumatic stress disorder (PTSD) and trauma-exposed healthy controls (TEHC). Statistical tests are adjusted for age, sex, and education in years

	PTSD ($n=44$)		TEHC ($n=26$)		Difference Between Groups		
Variables	n	Mean ± SD or %	n	Mean ± SD or %	t	df	p
$A\beta_{40}$	44	93.18 ± 56.13	26	105.84 ± 51.63	–0.75	63	0.46
$A\beta_{42}$	44	7.77 ± 4.59	25	8.1 ± 4.59	–0.49	63	0.63
Total tau	44	0.47 ± 0.43	26	0.5 ± 0.32	–0.29	63	0.77
$A\beta_{42}/A\beta_{40}$	44	0.09 ± 0.03	25	0.08 ± 0.03	1.10	63	0.27

Alzheimer's disease biomarker levels in PTSD and TEHC participants

Blood serum was collected from both PTSD and TEHC subjects and frozen at –80°C for an average of 1.6 years. Neither sample storage duration nor the age at which serum samples were collected significantly differed between PTSD and TEHC participants. As shown in Table 3, there were no significant between-group differences in serum $A\beta_{40}$ (TEHC 105.8 ± 51.6 versus PTSD 93.2 ± 56.1 pg/mL, $p=0.46$), $A\beta_{42}$ (TEHC 8.1 ± 4.6 versus PTSD 7.8 ± 4.6 pg/mL, $p=0.63$), $A\beta_{42}/A\beta_{40}$ ratio (TEHC 0.08 ± 0.03 versus PTSD 0.09 ± 0.03, $p=0.27$), or total tau

(TEHC 0.5 ± 0.3 versus PTSD 0.5 ± 0.4 pg/mL, $p = 0.77$). Likewise, there were no significant age x biomarker interactions between groups.

Interactions between biomarker levels and group status on neurocognitive variables

Finally, interaction effects of amyloid and tau serum concentrations and PTSD group status on cognitive functioning were considered. After controlling for age, sex, and educational attainment, no significant interactions between group and biomarker concentrations were found.

DISCUSSION

In summary, the findings of this investigation of AD serum biomarkers among older adults with chronic PTSD and matched TEHCs were null: participants with PTSD were not shown to differ from TEHCs on serum levels of $A\beta_{40}$, $A\beta_{42}$, the $A\beta_{42}/A\beta_{40}$ ratio, or total tau levels. Moreover, deleterious relationships between the biomarkers studied and cognitive outcomes were not stronger among PTSD participants compared to TEHCs. Thus, findings from this study did not support amyloid- or tau-related neurodegeneration as a mechanism for the strong epidemiologic relationships observed between PTSD and cognitive decline/dementia across samples.

These findings are consistent with some prior studies investigating relationships between PTSD and AD biomarkers, while being inconsistent with others. For example, preliminary reports from the ADNI dataset found *lower* odds of amyloid positivity based on cortical amyloid standardized uptake value ratio (SUVR) in the PTSD group relative to the controls despite significantly worse cognitive functioning being present among individuals with PTSD relative to controls [16]. Subsequent voxel-based reanalysis of the ADNI data found significant clusters dispersed across the brain for which SUVR was significantly higher among PTSD participants relative to controls, but the lack of significant differences observed between larger brain regions (i.e., five brain lobes) obscures the interpretation of these findings [17]. While studies of World Trade Center respondents have found suggestions of increased AD pathology and links between AD pathology and decreased cognition within these individuals, these studies did not include well-matched, contemporaneous controls. Therefore, it remains unknown whether the relationships observed would hold just as well among TEHCs and not be a pathophysiology specific to PTSD.

Given these findings, one alternative possibility is that cerebrovascular disease, rather than amyloid- and tau-associated neurodegeneration alone, contributes significantly to cognitive decline and dementia associated with PTSD. Decreased cortisol signaling associated with PTSD stimulates inflammatory cytokine production by means of reciprocal modulation occurring between the HPA axis and immune system [23, 24], which in turn is linked to adverse structural and functional changes in the aging central nervous system, including increased white matter hyperintensity (WMH) burden [25]. Higher levels of WMH are associated with increased risk for cognitive decline and dementia [26], and vascular factors such as WMH are increasingly recognized to be involved with late-onset AD pathogenesis [27, 28]. A recent study of 93 Holocaust survivors suffering from PTSD found that vascular dementia predominated over AD and other subtypes among the subgroup of demented participants [29]. Thus, future studies may investigate inflammation and subsequent vascular lesions as an important pathway to dementia among older adults with PTSD, whether independently through vascular dementia or as a moderator of ongoing AD-type neurodegeneration.

Alternatively, other types of neuropathology may be relevant to cognitive decline among individuals with PTSD. For example, brain changes underlying onset of dementia in PTSD could reflect a complex combination of neuropathologies not resembling any pure form of dementia. Such complexity has been observed in small case series combining neuroimaging with post-mortem laboratory methods [30] and may help explain observed inconsistencies in subtyping neurocognitive disorders in late-life PTSD patients. At this time more data are needed since the pathology underlying increased risk of neurodegeneration in PTSD and subsequent brain atrophy has begun to be investigated only recently.

Future studies enrolling larger samples of older adults with PTSD and age- and sex-matched TEHCs will be needed to reveal the pathophysiology underlying the phenomenon of accelerated cognitive decline in PTSD. Ideally, these studies will incorporate comprehensive neurocognitive assessment and include brain MRI as well as amyloid-based PET and or analysis of fluid biomarkers. We believe that this study represents a valuable contribution to this literature given the well-matched sample of PTSD participants

and matched TEHCs, which is uncommon among studies published to date. The present study also utilized comprehensive cognitive testing using a well-validated tool.

Against these strengths, the present findings must be interpreted in light of several limitations. First, this study was adequately powered to detect medium to large effect size differences (effect size 0.7 or greater) in blood-based AD biomarkers between PTSD and TEHC participants, which are of similar magnitude to previously published significant findings [18]. Smaller between-group effect size differences would require larger samples to evaluate. Another limitation is posed by the lack of apolipoprotein E (*APOE*) genotyping in the present study, as an asymmetry in the presence of the *APOE* E4 allele may have obscured a significant difference between the study groups (i.e., increase frequency of *APOE* E4 among TEHCs relative to PTSD participants). Furthermore, we only had serum available for analysis in this study, rather than plasma or cerebrospinal fluid. In general, plasma measurements of $A\beta_{42}$, $A\beta_{40}$, and tau, are higher than serum measurements, and assay performance in terms of robustness in the face of varying pre-analytics is superior in plasma, compared to serum [31]. Mitigating the effects of this limitation, assay performance for serum remains good, particularly for $A\beta_{40}$, $A\beta_{42}$, and the $A\beta_{40}/A\beta_{42}$ ratio. Normalizing $A\beta_{42}$ to $A\beta_{40}$ provides a more sensitive and specific measure of amyloid pathology than $A\beta_{42}$ level alone [32–34]. Nonetheless, it is possible that different results might be found by analyzing plasma and cerebrospinal fluid samples in addition to serum and/or the additional use of plasma phospho-tau as a biomarker (not available for serum). Lastly, traumatic brain injury is common among individuals with PTSD, particularly in Veterans, and was a basis for exclusion in this study, thereby potentially limiting the generalizability of our findings.

In summary, the present manuscript contributes to unfolding research focused on identifying the neuropathological processes underlying cognitive decline and progression to dementia among midlife and older adults with PTSD. Here, we found no evidence for increased levels of amyloid and tau biomarkers in serum samples taken from individuals with chronic PTSD compared to age- and sex-matched TEHCs. Future studies should continue to assess neurodegenerative mechanisms in PTSD employing comprehensive cognitive assessments, well-matched control groups, and neuroimaging and/or fluid biomarker assays.

ACKNOWLEDGMENTS

The authors have no acknowledgements to report.

FUNDING

This study was funded by a National Institute for Mental Health R01 MH111596 (Rutherford) and the Aging Gift Fund (Rutherford).

CONFLICT OF INTEREST

The authors have no conflicts of interest to report.

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