

Featured Article

Effects of traumatic brain injury and posttraumatic stress disorder on development of Alzheimer's disease in Vietnam Veterans using the Alzheimer's Disease Neuroimaging Initiative: Preliminary report

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Abstract

Introduction: Traumatic brain injury (TBI) and posttraumatic stress disorder (PTSD) have previously been reported to be associated with increased risk of Alzheimer's disease (AD). We are using biomarkers to study Vietnam Veterans with/without mild cognitive impairment with a history of at least one TBI and/or ongoing PTSD to determine whether these contribute to the development of AD. **Methods:** Potential subjects identified by Veterans Administration records underwent an initial telephone screen. Consented subjects underwent clinical evaluation, lumbar puncture, structural magnetic resonance imaging, and amyloid positron emission tomography (PET) scans.

Results: We observed worse cognitive functioning in PTSD and TBI + PTSD groups, worse global cognitive functioning in the PTSD group, lower superior parietal volume in the TBI + PTSD group, and lower amyloid positivity in the PTSD group, but not the TBI group compared to controls without TBI/PTSD. Medial temporal lobe atrophy was not increased in the PTSD and/or TBI groups.

Discussion: Preliminary results do not indicate that TBI or PTSD increase the risk for AD measured by amyloid PET. Additional recruitment, longitudinal follow-up, and tau-PET scans will provide more information in the future.

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Keywords:

Traumatic brain injury; Posttraumatic stress disorder; Alzheimer's disease; Vietnam veterans; Mild cognitive impairment

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1. Introduction

Alzheimer's disease (AD) is characterized by the presence of amyloid plaques and tau fibrils, which are associated with synaptic loss and neurodegeneration, leading to cognitive impairments and dementia. After age, family history, and apolipoprotein E (*APOE*) $\epsilon 4$ risk allele [1], traumatic brain injury (TBI) has been reported as a risk factor in many [2–33] but not all [13] epidemiological studies (reviewed in [34–36]). Some studies have suggested that a history of TBI is associated with earlier onset of AD [3,6,13,18,20,34,35,37]. Others, but not all, have shown an interaction of TBI with the *APOE* $\epsilon 4$ allele [5,6,15,17,38–46]. After TBI, young subjects appear to have had A β pathology in postmortem brain tissue [47,48]. A comprehensive consensus analysis of the literature concluded that there was some evidence for a relationship between TBI in males and future development of AD (odds ratio 2.29 [1.47–3.58]) [20]. One study [33], which showed a significantly increased risk of developing AD after TBI, used information provided by the US Department of Defense to identify and prospectively enroll subjects with nonpenetrating head injury suffered during WWII and the Korean War, and non-head-injured controls. Recently, one study from the Mayo Clinic Study of Aging [49] suggested that MCI, but not cognitively normal subjects, who reported a history of concussion had higher brain A β levels, measured with A β positron emission tomography (PET) scans, than noninjured MCI participants. With the exception of one publication [50], studies of the effects of TBI on AD have used “self-report” information to determine a history of concussion; few studies have used imaging and cerebrospinal fluid biomarkers to investigate the relationship of TBI to AD.

Posttraumatic stress disorder (PTSD) is an anxiety disorder following exposure to traumatic stress [51]. The prevalence of combat-related PTSD in US military Veterans since the Vietnam War ranges from 10% to 15% [52,53]. PTSD is associated with worse cognitive functioning [50,54–62]. Furthermore, PTSD is associated with alterations in the hippocampus [63–67], anterior cingulate [65], and prefrontal structures [63–69], whereas improvement of symptoms is associated with less-progressive atrophy [67]. The relationship of PTSD to impaired cognitive function and hippocampal abnormalities suggests that PTSD could be a risk factor for the development of AD. A study of the national Veterans Administration (VA) clinical database showed that Veterans with PTSD are twice as likely to develop a dementia diagnosis compared to Veterans without PTSD, even when controlling for known risk factors for dementia [70]. Aside from magnetic resonance imaging (MRI) studies, to our knowledge, there are no reports of the use of A β PET scans or other biomarkers to examine whether the mechanism accounting for the higher risk for dementia in PTSD is related to AD pathology.

The Alzheimer's Disease Neuroimaging Initiative (ADNI) is a large, multisite study, aimed at validating biomarkers for AD clinical trials. ADNI has enrolled over 1500 subjects at 57 sites in the United States and Canada and followed them

longitudinally with clinical/cognitive testing, genetic analysis, MRI, lumbar puncture for cerebrospinal fluid (CSF) analysis, ^{18}F -fluorodeoxyglucose PET, A β PET, and most recently tau-PET (reviewed in [71]). To investigate the relationship of a past history of TBI and PTSD on the development of AD, the Department of Defense funded three proposals: (1) Effects of Traumatic Brain Injury (TBI) and Posttraumatic Stress Disorder on Alzheimer's Disease in Veterans Using Imaging and Biomarkers in the AD Neuroimaging Initiative; (2) Effects of Traumatic Brain Injury and Posttraumatic Stress Disorder on Alzheimer's Disease in Veterans with Mild Cognitive Impairment Using the Alzheimer's Disease Neuroimaging Initiative; and (3) Effects of Traumatic Brain Injury and Posttraumatic Stress Disorder and Alzheimer's Disease on Brain Tau in Vietnam Veterans Using ADNI. These studies are collectively termed “DOD ADNI,” and aim to enroll approximately 400 elderly Veterans who served in Vietnam.

The initial DOD ADNI grant enrolled Vietnam Veterans with PTSD and/or TBI, as well as controls with service-connected disorders not related to PTSD or TBI who met criteria for normal cognition. The second grant expanded the original study to include subjects who also met criteria for MCI. The study now includes cohorts of Vietnam Veterans, both with and without MCI, who have histories of TBI, PTSD, and both TBI and PTSD, as well as controls without PTSD/TBI. Potential subjects are initially contacted by mail, prescreened for eligibility by telephone and those meeting criteria for one of the cohorts are referred for clinical examination, cognitive tests, A β PET using ^{18}F -labeled florbetapir, MRI (structural, diffusion tensor, and resting state functional), lumbar puncture for CSF markers of tau, phosphorylated tau (p-tau₁₈₁), β -amyloid (A β 42), and blood collection for genetic analysis. The clinical/cognitive battery and MRI is repeated after 1 year, and tau-PET scans are obtained at baseline and after 1 year. Results from the CSF assays and tau-PET imaging are pending and will not be reported in this article.

This interim report uses baseline data to determine the extent to which a prior history of TBI and/or documented past history and present diagnosis of PTSD increase the risk of developing AD. Our primary a priori hypothesis is that Vietnam Veterans with a history of TBI or presence of ongoing PTSD will have lower cognitive functioning and increased prevalence of brain AD pathology (measured by A β florbetapir PET and medial temporal lobe atrophy) after accounting for effects of age and presence of the *APOE* $\epsilon 4$ allele.

2. Methods

2.1. Identification of potential study subjects

For this study, we used an operational definition of TBI as head injury with loss of consciousness for more than 5 minutes, and/or having amnesia, and/or being dazed and confused for more than 24 hours. Using military and VA Compensation

and Pension records, as well as VA Health records, and/or response to advertisements, Vietnam Veterans with a service connection related to a possible traumatic head injury and/or a history of at least one moderate/severe TBI and/or evidence of ongoing PTSD, and demographically comparable Veteran controls without PTSD/TBI were identified. Because TBI was not a common diagnostic code during the Vietnam War, the study requested a sample of subjects from the Veteran Benefits Administration who were service-connected for several diagnostic codes that might be related to a traumatic brain injury (traumatic brain disease, posttrauma headache, acute posttrauma headache, chronic posttrauma headache, post-concussion syndrome, brain hemorrhage, limited motion of the jaw, and other head-related injuries). We also obtained separate samples of subjects who are service-connected for PTSD as well as a sample of controls who were service-connected for something other than PTSD or TBI. Study invitation letters, brochures, and response postcards were mailed to Veterans who met these initial broad criteria and who lived within 150 miles of the closest ADNI clinic.

2.2. Initial telephone prescreening recruitment calls

To include all subjects who may have a history of a TBI and to confirm whether or not the TBI-related diagnostic codes were related to a head injury, all subjects were contacted by telephone, and verbal consent was obtained for the administration of screening questions which determined eligibility criteria for current PTSD symptoms and history of a TBI. The Ohio State University TBI Identification Method–Interview Form [72] was used to ask about head injuries at three separate times in a subject's life: before, during, and after Vietnam. This ensured we included TBIs that may have occurred before or after a subject's military service. In addition, a safety assessment ruled out subjects who were not safe to participate in the study procedures. The purpose of the initial telephone prescreening recruitment call was both to (1) rule out exclusions such as dementia, history of psychosis or bipolar affective disorder, history of schizophrenia (*Diagnostic and Statistical Manual of Mental Disorders, 4th edition* criteria), history of alcohol or substance abuse/dependence within the past 5 years, MRI-related exclusions (metal in the body, pacemakers), contraindications for lumbar puncture, PET scan, or other procedures in this study and (2) assess placement in study cohorts. During this initial screen, MCI was assessed using an adapted version of the AD8 (70, 71) and the Telephone Interview for Cognitive Status, as the latter contains a 10-word list recall which combined with the AD8 can help to identify cognitive impairment [73,74]. Subjects meeting inclusion criteria were then mailed a written consent form for the telephone psychiatric assessment (clinical interview) portion of the study and audio recording, with a stamped addressed return envelope and the following self-report questionnaires: (1) MRI safety, (2) Medical history, (3) Current medications, (4) Symptom Check List 90 (revised) for general psychopathology [75], (5) Pittsburgh Sleep Quality [76], (6) Smoking/Life Time

Smoking, (6) SF-12 Health Survey [77], and (7) Combat Exposure Scale [78].

After documented consent was received, all self-report questionnaires described previously were reviewed as well as the subjects' VA medical records to ensure that there were no medical problems or exclusionary medications that the subject failed to report and to ensure that proper cohort assignment had been determined. VA medical records were reviewed for any documentary evidence of a TBI at anytime in a subject's life regardless of whether or not a subject reported a TBI during the administration of the Ohio State University TBI Identification Method–Interview Form. If the medical records specifically mentioned a TBI incident or a service connection related to a TBI (as indicated by the diagnostic codes discussed previously), or if a subject self-reported a TBI (that met the operational criteria of TBI discussed previously) during anytime in the subject's life, this subject was not placed in the control group.

2.3. SCID CAPS evaluation by telephone

All eligible subjects were next referred to the telephone clinical evaluation which used the Structured Clinical Interview 1 of the *Diagnostic and Statistical Manual of Mental Disorders, Version IV, (Axis 1)–Text Revision (SCID)* and the *Clinician Administered PTSD Scale for DSM-IV (CAPS)* [79] to assess current and lifetime PTSD and to rule out psychosis and/or drug and alcohol issues. SCID CAPS, as well as the *Life Stressor Checklist* [80] and the *Addiction Severity Index Lite* [81], was conducted by telephone by the PTSD Core at the San Francisco Veterans Administration Medical Center.

2.4. Assignment of subjects to cohorts

After completing the SCID CAPS, eligible subjects were placed into one of eight cohorts, four with no MCI and four who met initial criteria for MCI, as described in the following:

- TBI only: Subjects with no service connection for PTSD, no history of lifetime, and/or current PTSD on SCID CAPS (scores of <30 for each) but with a service connection for a TBI-related diagnostic code, medical documentation of a TBI-related incident, and/or a self-report of a TBI which met the operational definition of TBI described previously.
- PTSD only: Subjects who were service-connected for PTSD and who scored ≥ 40 for both lifetime and current PTSD, with no self-report history of TBI, no diagnostic service connection related to TBI, and no medical documentation of TBI.
- Both TBI + PTSD: Subjects who scored ≥ 30 for either lifetime and/or current PTSD and had a service connection related to TBI, medical documented evidence of a TBI-related incident, and/or a self-report history of TBI meeting the operational criteria of TBI described previously.

- Controls: Subjects with no service connection for PTSD, no history of lifetime, and/or current PTSD on SCID CAPS (scores of <30 for each), and no service connection for TBI-related diagnostic codes, no medical documentation of a TBI-related incident, and no self-report of a TBI that met the operational definition of TBI.

Eligible subjects were next referred to one of the 19 ADNI Clinic sites to sign a clinic consent and complete study procedures.

2.5. Clinical evaluation, neuropsychological testing, MRI, and A β florbetapir PET scans

After the clinical telephone interview, subjects were referred to the closest ADNI site for in-person studies using the identical methods used by ADNI. These include clinical evaluation, neuropsychological testing, lumbar puncture (results not available at this time), genetic sampling for the *APOE* ϵ 4 allele, structural MRI at 3T, and A β florbetapir PET scans. These methods have been widely reported [82–86]. Longitudinal data and tau-PET scan results will be reported at a later time.

2.6. Power analysis

Our original study was designed to have 80% power to detect a minimum difference in means of 0.55 standard deviations, assuming 65 participants in each group, an alpha of 0.025, and a two-sided test. In this interim report, we have not yet achieved our desired sample size in each group, particularly in the TBI and TBI + PTSD groups. For comparison of the TBI group ($n = 22$) with the no TBI/PTSD group ($n = 63$), we have 80% power to detect a difference as small as 0.78 standard deviations (0.68 standard deviations for the TBI + PTSD vs. no TBI/PTSD group). Minimum detectable differences are larger for the imaging outcomes, where sample sizes are even smaller.

2.7. Statistical analysis

Means and standard deviations were computed for all continuous variables of interest (age, education, neuropsychological testing, MRI volumetrics, and florbetapir standardized uptake value ratio [SUVR]), whereas percentages were calculated for categorical variables (gender, race/ethnicity, diagnosis, *APOE* ϵ 4 status). Analysis of variance or Fisher's exact test was used to compare groups (PTSD, TBI, both, neither) on demographic and clinical characteristics. Linear regression was used to compare groups on most neuropsychological testing scores and MRI volumetrics. Volume of white-matter hyperintensities was transformed with natural log to meet the assumptions of the models. Poisson regression [87] was used to compare groups on the clinical dementia rating (CDR) Sum of Boxes because this outcome did not meet the assumptions of linear regression. Mini-Mental State

Examination (MMSE) was rescaled as the number of errors (30 MMSE) and analyzed with a negative binomial regression due to overdispersion. Finally, logistic regression was used to compare amyloid positivity based on A β florbetapir cortical SUVR across the groups. All models were adjusted for age, education, and *APOE* ϵ 4 status by including these variables in the models. Primary comparisons of interest for all analyses were between the patient groups (PTSD, TBI, both) and the control group (no PTSD or TBI). All analyses were conducted using SAS software version 9.4 [88] with a P -value <.05 considered statistically significant.

3. Results

3.1. Description of the recruitment assessment process

The number of subjects contacted by mailing brochures, the initial telephone screening effort, including number of subjects called and screened, the numbers of consents mailed and SCID evaluations by telephone, and finally the number of completed baseline clinic visits and 12-month follow-up visits are outlined in Fig. 1.

3.1.1. Demographic and clinical characteristics

The demographic and clinical characteristics of the cohort are given in Tables 1 and 2. The groups differed in age, with the control group without PTSD/TBI significantly older than the PTSD ($P < .001$), TBI ($P = .005$), and TBI + PTSD ($P < .001$) groups. Education also differed between the groups, with the PTSD group significantly less educated than the control group ($P = .004$). There were no differences in gender, race/ethnicity, or *APOE* ϵ 4 allele status. The percentage of subjects with an MCI diagnosis was significantly different across the groups ($P = .03$), with a significantly higher percentage in the group with both TBI and PTSD and the group with PTSD than in the controls.

In models adjusted for age, education, and *APOE* ϵ 4 allele status, there was no significant difference in verbal memory (RAVLT, Delayed Recall), but there was a trend for a difference in global cognition (MMSE, ADAS-Cog) with the PTSD group having worse global cognition than the controls. There was a significant difference in CDR Sum of Boxes, with the PTSD group ($P = .009$) and the TBI + PTSD group ($P = .007$) having higher CDR Sum of Boxes scores (indicating worse cognitive functioning) than the controls. This finding and the trend for worse global cognitive function remained even after further accounting for amyloid burden in the brain as measured by A β florbetapir PET (MMSE: PTSD vs. control: $P = .052$; CDR Sum of Boxes: PTSD vs. control: $P = .03$, TBI + PTSD vs. control: $P = .008$).

3.2. Brain structure measured by MRI

Table 3 describes the brain regional volumes and volume of white-matter hyperintensities across the groups. There were no significant differences between the groups in models

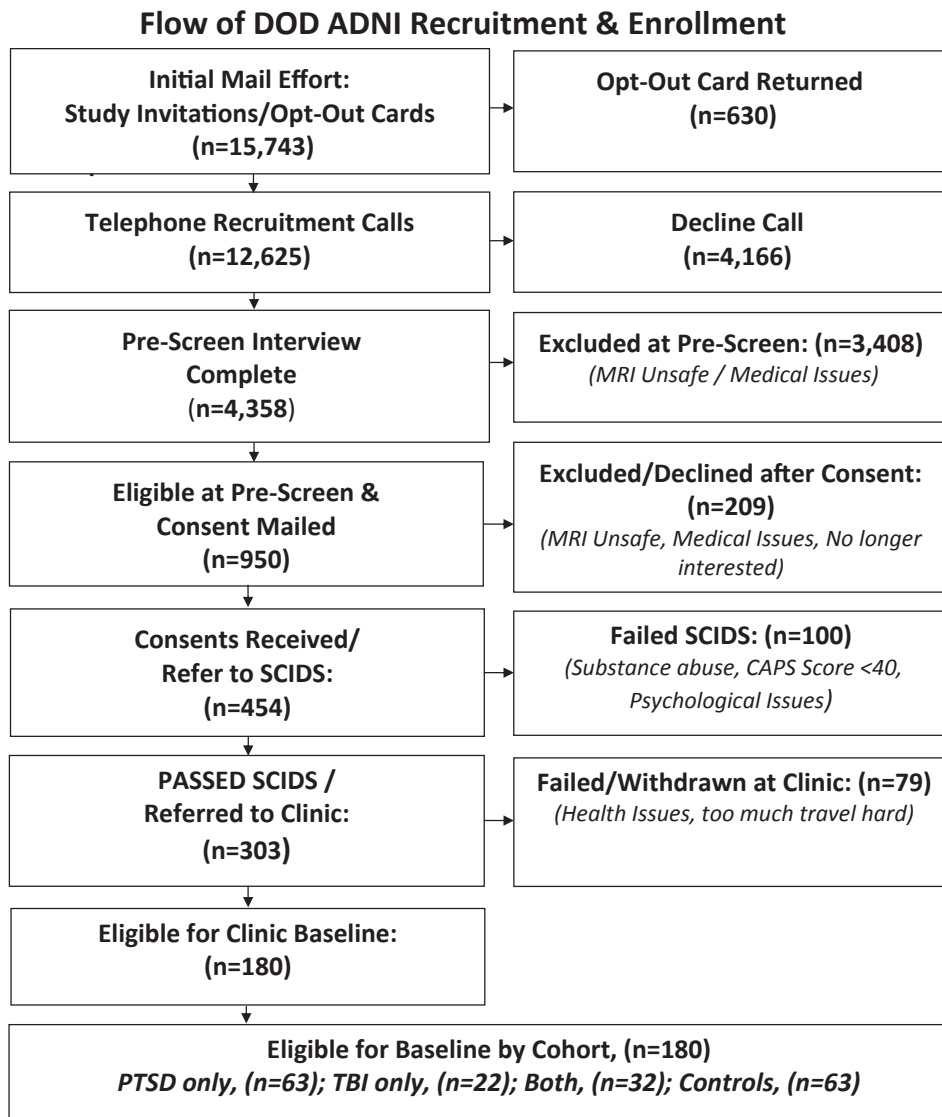


Fig. 1. Overall summary of study recruitment and enrollment. Abbreviations: ADNI, Alzheimer's Disease Neuroimaging Initiative; PTSD, posttraumatic stress disorder; TBI, traumatic brain injury.

adjusted for age, education, and *APOE* $\epsilon 4$ allele status except in the superior parietal region ($P = .046$), which had a slightly lower volume in the TBI + PTSD group than in the control group ($P = .04$). A further analysis that considered a measure of PTSD (CAPS) rather than the specific exposure groups found no association between level of PTSD and hippocampal volume ($P > .7$) or superior parietal volume ($P > .3$) for either the current CAPS or lifetime CAPS, in a model that included age, education, and *APOE* $\epsilon 4$ allele status.

3.3. β amyloid florbetapir positron emission tomography

Table 4 and Fig. 2 illustrate the distribution of $A\beta$ florbetapir cortical SUVR across the groups. When categorized according to amyloid positivity using a previously validated cutoff of 1.11 [89], there was a significant difference by group ($P = .04$) in a model adjusted for age, education, and *APOE*

$\epsilon 4$ allele status, with the PTSD group having significantly lower odds of being amyloid positive (odds ratio: 0.21; 95% CI: 0.05–0.93; $P = .04$) than the controls. The proportion of controls in this study classified as amyloid positive was comparable to previous ADNI studies (data not shown).

4. Discussion

The major findings of this project are as follows: (1) worse cognitive functioning as measured by the CDR Sum of Boxes in the PTSD and both TBI + PTSD groups relative to the controls; (2) a trend for worse global cognitive functioning (ADAS-Cog, MMSE) in the PTSD group relative to the controls; (3) slightly lower superior parietal volume in the group with both TBI + PTSD relative to controls; (4) lower odds of amyloid positivity based on cortical amyloid SUVR in the PTSD group relative to the

Table 1
Participant characteristics

	No TBI/PTSD (<i>n</i> = 63)	PTSD (<i>n</i> = 63)	TBI (<i>n</i> = 22)	TBI + PTSD (<i>n</i> = 32)	<i>P</i> value*
Age	71.1 (5.9)	67.8 (3.6)	67.9 (4.5)	68.7 (3.1)	<.001
Education	16.0 (2.2)	14.7 (2.5)	15.8 (2.2)	15.2 (2.4)	.01
Male (%)	100	100	100	96.9	.30
Ethnicity (%)					.81
African American	6.3	4.8	9.1	12.5	
Asian	4.8	0	0	0	
Caucasian	80.9	82.5	81.8	78.1	
Hispanic	6.3	11.1	9.1	9.4	
Other	1.6	1.6	0	0	
E4+ (%) [†]	25.9	30.4	36.8	29.6	.81
MCI (%) [‡]	3.3	15.5	10.0	20.7	.03

Abbreviations: TBI, traumatic brain injury; PTSD, posttraumatic stress disorder; E4+, carriers of the $\epsilon 4$ allele of apolipoprotein E; MCI, mild cognitive impairment.

NOTE. Means and standard deviations are presented unless otherwise stated.

**P* value presented is for the overall group difference.

[†]E4 data available for all but 5 No TBI/PTSD (controls), 7 PTSD, 3 TBI, and 5 TBI + PTSD.

[‡]Diagnosis available for 61 No TBI/PTSD, 58 PTSD, 20 TBI, and 29 TBI + PTSD.

controls; and (5) no evidence for increased brain amyloid associated with TBI and no evidence for medial temporal lobe atrophy in those with PTSD and/or TBI relative to the controls. Taken together, these results do not support the hypothesis that prior TBI or PTSD is associated with increased brain amyloid. Furthermore, the worse cognitive functioning in the PTSD and TBI + PTSD groups is not associated with increased brain amyloid. Overall, this interim analysis of an ongoing study does not support the view that TBI or PTSD is associated with increased development of AD.

Our first finding of worse cognitive functioning in the PTSD group confirms previous reports [90–94]. Furthermore, at least one previous study indicates that PTSD is associated with an increased incidence of dementia [95]. However, there are no autopsy reports demonstrating increased AD pathology in Veterans with PTSD. Moreover, levels of white-matter hyperintensities did not differ among groups suggesting that the worsening cognitive function in the PTSD group is not explained by cerebrovascular disease. Therefore, the cause of cognitive decline or dementia in

Veterans with PTSD is not known. The interim results of our ongoing study do not show increased brain amyloid in the PTSD group compared to controls. In fact, there is a trend for reduced brain amyloid in the PTSD group. Although these results are preliminary, they suggest that the cognitive impairment and dementia associated with PTSD may not be due to AD pathology.

Hippocampal atrophy has been associated with PTSD in some studies [66,96–98], but not others [99–102]. Hippocampal atrophy is typically found in AD dementia but is not specific for this condition [103]. Therefore, our failure to detect hippocampal atrophy in the PTSD or TBI + PTSD group in this study further suggests that the cognitive impairments in the PTSD subjects are not due to AD pathology.

Thus far, our study shows no evidence for increased brain amyloid load in subjects with prior history of TBI or TBI + PTSD in contrast with previous reports of TBI as a risk factor for AD. In contrast to most of these reports which used “self-reported” TBI, we identified subjects from the VA

Table 2
Neuropsychological performance by group

	No TBI/PTSD (<i>n</i> = 63)	PTSD (<i>n</i> = 63)	TBI (<i>n</i> = 22)	TBI + PTSD (<i>n</i> = 32)	<i>P</i> value*
ADAS-Cog [†]	10.9 (4.6)	12.8 (3.9)	9.4 (3.6)	11.0 (5.2)	.10
MMSE	28.7 (1.3)	28.0 (1.7)	28.8 (1.1)	28.4 (1.5)	.14
CDR Sum of Boxes [‡]	0.19 (0.40)	0.62 (0.82)	0.33 (0.56)	0.47 (0.81)	.02
RAVLT [§]	41.3 (9.2)	39.3 (7.4)	41.3 (9.4)	41.2 (9.1)	.46
Delayed Recall	11.1 (3.8)	9.7 (3.8)	10.9 (3.3)	11.2 (4.1)	.63

Abbreviations: TBI, traumatic brain injury; PTSD, posttraumatic stress disorder; ADAS-cog, Alzheimer's Disease Assessment Scale–cognitive; MMSE, Mini-Mental State Examination; CDR, clinical dementia rating; RAVLT, Rey's auditory verbal learning test.

NOTE. Means and standard deviations are presented.

**P* value presented is for the overall group difference in models that adjust for age, education, and *APOE* $\epsilon 4$ allele status.

[†]Total score based on 13 items; missing for 1 No TBI/PTSD, 3 PTSD, 1 TBI, and 1 TBI + PTSD.

[‡]Missing for 2 No TBI/PTSD, 3 PTSD, 1 TBI, and 1 TBI + PTSD.

[§]Rey Auditory Verbal Learning Test: sum of five trials; missing for 1 No TBI/PTSD, 3 PTSD, 1 TBI, and 1 TBI + PTSD.

^{||}Logical Memory II.

Table 3
MRI volumetrics by group

	No TBI/PTSD (n = 52)	PTSD (n = 37)	TBI (n = 16)	TBI + PTSD (n = 15)	P value*
Hippocampus [†]	0.51 (0.06)	0.53 (0.06)	0.52 (0.05)	0.51 (0.08)	.81
Entorhinal cortex [†]	0.26 (0.04)	0.28 (0.04)	0.28 (0.02)	0.27 (0.03)	.56
Inferior parietal [†]	1.70 (0.17)	1.74 (0.18)	1.82 (0.15)	1.77 (0.13)	.21
Superior parietal [†]	1.64 (0.16)	1.69 (0.20)	1.71 (0.15)	1.56 (0.13)	.046
Inferior temporal [†]	1.38 (0.15)	1.44 (0.14)	1.41 (0.15)	1.36 (0.12)	.35
Superior temporal [†]	1.42 (0.15)	1.44 (0.15)	1.41 (0.18)	1.47 (0.15)	.71
White-matter hyperintensities [‡]	6.1 (6.4)	4.4 (3.8)	5.0 (5.5)	4.0 (3.9)	.47

Abbreviations: MRI, magnetic resonance imaging; TBI, traumatic brain injury; PTSD, posttraumatic stress disorder.

NOTE. Means and standard deviations are presented.

*P value presented is for the overall group difference in models that adjust for age, education, and APOE ε4 allele status.

[†]Expressed as percentage of intracranial volume.

[‡]White-matter hyperintensities data based on 59 No TBI/PTSD, 53 PTSD, 18 TBI, and 21 TBI + PTSD participants.

records who receive VA compensation for diagnostic codes that might be related to a traumatic brain injury as well as by self-report of TBI before, during, and after Vietnam. In addition, there are no previous studies using Aβ florbetapir PET to determine brain amyloid load, or MRI to detect hippocampal atrophy in elders with a past history of TBI. One study reported greater amyloid deposition in MCI subjects measured by amyloid PET using Pittsburgh compound B but head trauma was again self-reported [49]. Although AD is considered an amyloid-mediated tauopathy, and we have yet to analyze CSF tau levels or tau-PET imaging results, our findings thus far lead us to conclude that we have not found evidence of a connection between past history of TBI and development of amyloid pathology characteristic of AD. The present study suggests that TBI may be associated with cognitive decline unrelated to AD and is, in this regard, consistent with a report [104] instead showing an association of TBI with an increased risk of Parkinson's disease.

5. Limitations of the study

We wish to emphasize the limitations of this interim report. The first limitation is the small sample size of the TBI group. Many Veterans who were contacted did not return our calls, declined to participate, or were unable to participate for a variety of reasons. Compared to subjects who were excluded or declined, the baseline subjects were slightly younger, and there were more Caucasians, fewer African Americans, and more Latinos. Furthermore, for unknown reasons, African American Veterans had a higher "passive refusal rate" (less likely to answer the phone, return phone calls, keep an

appointment, return consent forms, etc.). These results reflect a combination of factors including willingness to participate and comorbidities which led to exclusions. Therefore, the population which was studied in the clinic differs considerably from the population of subjects who were initially contacted for this project. Despite our efforts to contact and enroll all Vietnam Veterans receiving compensation from the VA diagnostic codes that may be related to TBI, we found that a very high proportion of Veterans with history of TBI had comorbidities which prevented them from enrolling in the study. In particular, we found that large numbers of these Veterans reported metal in the body, which prevented MRI examinations. The prevalence of this exclusion was much higher than we have experienced in civilian populations studied in ADNI. However, to increase the number of subjects, the decision was recently made to waive the MRI for subjects in the TBI/both cohorts, if the only reason for exclusion was that MRI was unsafe. In addition, Veterans with both TBI and PTSD had exclusions for many other reasons and overall the "screen fail" rate in this study is much higher than we have experienced with ADNI. These findings serve to emphasize the well-known observation that clinical research studies which impose strict inclusion/exclusion criteria to eliminate comorbidities run the risk of studying a sample that does not resemble the "general population." Furthermore, research studies which include biomarker measurements such as MRI, PET scans, and lumbar punctures also run the risk of reducing generalizability.

A second limitation is that our selection of cognitively normal and MCI participants able to be followed over the timeframe of the study, rather than of Veterans already

Table 4
Florbetapir cortical SUVR by group

	No TBI/PTSD (n = 54)	PTSD (n = 52)	TBI (n = 19)	TBI + PTSD (n = 21)	P value*
Cortical SUVR	1.07 (0.14)	1.01 (0.07)	1.08 (0.20)	1.06 (0.08)	.21
% amyloid positive (SUVR > 1.11)	24.1	5.8	21.0	33.3	.04

Abbreviations: SUVR, standardized uptake value ratio; TBI, traumatic brain injury; PTSD, posttraumatic stress disorder.

NOTE. Means and standard deviations are presented.

*P value presented is for the overall group difference in a model that adjusts for age, education, and APOE ε4 allele status.

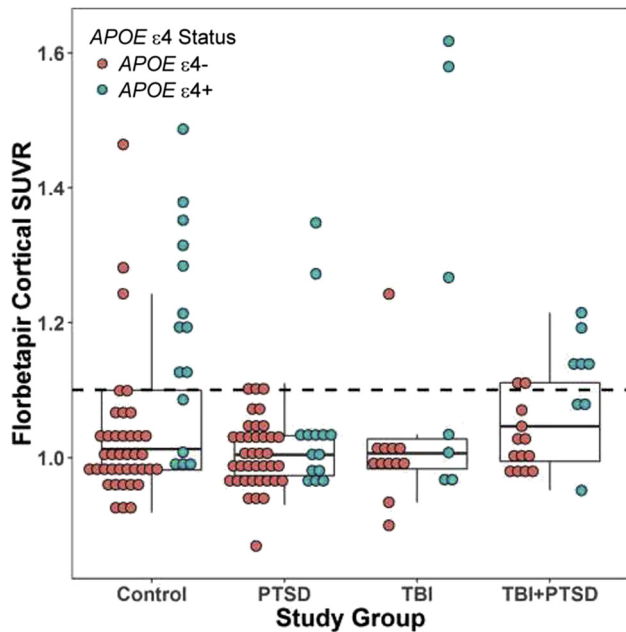


Fig. 2. Florbetapir cortical SUVR by group and *APOE* $\epsilon 4$ allele status. The dotted line represents a previously validated amyloid positivity cutoff of 1.11 [89]. Abbreviations: *APOE* $\epsilon 4$, apolipoprotein E $\epsilon 4$ allele; PTSD, post-traumatic stress disorder; SUVR, standardized uptake value ratio; TBI, traumatic brain injury.

exhibiting dementia, may automatically eliminate Veterans susceptible to the development of AD. The remaining cohort may represent a portion of the population that does not develop AD as a result of TBI and/or PTSD.

It is important to emphasize that this is an interim analysis of an ongoing study. In addition to our continued enrollment and baseline assessments, we are obtaining 12-month follow-up data. We are also performing tau-PET imaging at baseline and 12-month follow-up. Our preliminary results do not support the hypothesis that either TBI or PTSD increases the risk for AD measured with biomarkers. Subjects with PTSD do appear to have worse cognition, but this is not associated with increased amounts of brain amyloid measured by $A\beta$ florbetapir PET scans. In the present study, we controlled for *APOE* genotype, the strongest genetic risk factor for late onset AD. In the future, genome-wide genotyping will be available so that other major candidate genes for AD, PTSD, and TBI can be assessed. When we complete enrollment, we will test the major hypotheses again, and the large sample size will provide sufficient statistical power for additional hypothesis testing and data exploration. Longitudinal data and tau-PET data will also be reported.

6. Conclusions

Epidemiological studies have inconsistently linked history of TBI or PTSD as risk factors for AD although few have investigated the relationship using imaging or CSF biomarkers. The study aims to determine the relationship between a history of TBI and/or PTSD and AD pathology.

This preliminary report includes results from baseline clinical examinations, cognitive tests, structural MRI, and $A\beta$ florbetapir PET imaging. Despite finding lower cognitive functioning in the PTSD and TBI + PTSD groups, and lower superior parietal volume in the TBI + PTSD group relative to controls, there was no evidence to suggest that the observed cognitive decline or atrophy was related to amyloid deposition. The study was limited by the small sample size of the TBI group and does not include results from ongoing tau-PET imaging or CSF biomarker analysis. However, we conclude that these interim results do not support the hypothesis that either TBI or PTSD increases the risk for AD as measured by biomarkers.

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RESEARCH IN CONTEXT

1. Systematic review: The authors reviewed literature pertaining to the associations between traumatic brain injury, posttraumatic stress disorder, and cognitive decline, and the incidence and prevalence of these risk factors in military populations using traditional sources such as PubMed.
2. Interpretation: Although we observed worse cognitive functioning in veterans with traumatic brain injury (TBI) and/or posttraumatic stress disorder, these risk factors did not increase AD risk measured by amyloid positron emission tomography (PET). Limitations include difficulty in recruitment due to exclusions resulting in a small sample size of TBI subjects and a study population that does not resemble the "general population."
3. Future directions: The study will continue to enroll participants and performed follow-up assessments of existing participants. Tau-PET imaging at baseline and 12 months will be performed and major hypotheses will be tested again.

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