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Elevated Tau in Military Personnel Relates to Chronic Symptoms Following Traumatic Brain Injury

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Abstract

Objective: To understand the relationships between traumatic brain injury (TBI), blood biomarkers, and symptoms of posttraumatic stress disorder (PTSD), depression, and postconcussive syndrome symptoms (PCS).

Design: Cross-sectional cohort study using multivariate analyses.

Participants: One-hundred-and-nine military personnel and Veterans, both with and without a history of TBI.

Main Measures: PTSD Checklist-Civilian Version (PCL); Neurobehavioral Symptom Inventory (NSI); Ohio State University TBI Identification Method; Patient Health Questionnaire-9 (PHQ-9); Simoa™-measured concentrations of tau, Amyloid-beta (Aβ40, −42, and NFL.

Results: Controlling for age, sex, time since last injury (TSLI) and anti-anxiety/depression medication use, NFL was trending towards being significantly elevated in participants who had sustained 3 or more TBIs compared to those who had sustained 1–2. Within the TBI group, partial correlations which controlled for age, sex, TSLI and anti-anxiety/depression medication use, showed that tau concentrations were significantly correlated with greater symptom severity, as measured with the NSI, PCL and PHQ-9.

Conclusions: Elevations in tau are associated with symptom severity after TBI, while NFL levels are elevated in those with a history of repetitive TBI, in military personnel and Veterans.

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This study shows the utility of measuring biomarkers chronically post-injury. Furthermore, there is a critical need for studies of biomarkers longitudinally following TBI.

Keywords

amyloid-beta; neurofilament light chain (NFL); biomarkers; post-traumatic stress disorder (PTSD); postconcussive symptoms; service members; veterans

Introduction

Traumatic brain injuries (TBIs) are common among military personnel and have been linked to high rates of chronic behavioral symptoms and neurological deficits, especially in those with multiple injuries.[1] Clinical outcomes following TBI may include global disability, neurobehavioral impairment, and psychological comorbidities.[2,3] Moreover, posttraumatic stress disorder (PTSD) and post-concussive syndrome (PCS) are highly prevalent among military personnel and Veterans and frequently occur comorbidly with TBI,[4,5] resulting in substantial health risks.[6] While most individuals recover from a TBI within months after the injury, others will endure persistent symptoms.[7] This variability in outcomes following TBI raises questions regarding the nature of vulnerability and the mechanisms that contribute to symptoms, especially symptoms that persist over time. It is hypothesized that in some individuals, TBIs initiate pathogenic processes that induce neuronal, glial, and endothelial cells to extracellularly release molecules that transit into the blood, which in turn influences the development of neurological and behavioral symptoms.[8] However, efforts to identify the specific mechanisms that underlie these symptoms have proven elusive. Elucidating the biological variances that are associated with TBIs featuring comorbid chronic PTSD and PCS may ultimately enable the identification of the neuronal mechanisms that underlie these symptoms in military personnel and Veterans to improve care and inform novel interventions.

Tau is a neuronal structural protein that regulates microtubules and stabilizes axons. Phosphorylated tau (p-tau) forms paired helical filaments and aggregates into the neurofibrillary tangles observed in neurodegenerative disorders.[9] Elevated blood tau concentrations were identified in service members with blunt force and blast exposures and the degree of elevation correlated with PCS symptom severity.[10] Other studies have also reported elevated blood tau concentrations after concussion, and even subconcussive impacts, that occurred during athletic activities,[11,12] and the degree of elevation correlated with prolonged return to play.[13] Additionally, repetitive hits to the head have been linked to chronic traumatic encephalopathy (CTE), a neurodegenerative condition, characterized by accumulation of neurofibrillary tangles, as well as neuronal and glial aggregates.[14]

Amyloid-beta (Aβ) is a cleavage product of amyloid precursor protein which has both neuroprotective and neurotoxic effects.[15] Aβ is known to be aggregated in neurodegenerative disorders, which may occur due to impaired clearance.[15] Aβ deposits have been found following severe and repetitive mild TBI, and have been linked to the pathological process and clinical progression of Alzheimer's Disease (AD), dementia and CTE.[15,16] Elevated blood levels of Aβ have been found in individuals with deployment-

related TBIs when compared to non-TBI controls.[17] Together with tau, Aβ are candidate biomarkers of TBI that have been hypothesized to play a role in the potentiation of TBI-related neurodegenerative disorders. Despite this evidence, the role of these biomarkers in relation to chronic TBI-related symptoms and outcomes remains to be understood.

Another hypothesized biomarker of chronic TBI is the neurofilament light (NFL) chain. NFL is a key protein in the formation of neurofilaments, which are structural elements of the neuronal cytoskeleton and axons.[18] Increased NFL levels in the blood and cerebrospinal fluid (CSF) reflect axonal damage due to brain injury and neurodegeneration.[19,20] NFL has also been shown to be elevated in a variety of neurodegenerative diseases such as AD and frontotemporal dementia.[21] Increased NFL levels in the blood and CSF have been observed in a full range of TBIs, from mild to severe.[22–24] Blood levels of NFL in patient samples collected within 24 hours of a TBI were higher in subjects with abnormal head computed tomography (CT) when compared to individuals with normal head CT.[25] Moreover, higher NFL levels in the blood during the acute post-TBI period have been associated with worse functional recovery.[26] Despite recent progress, the informative potential of NFL in chronic symptoms following a TBI has yet to be fully determined.

Current research indicates that sustaining multiple TBIs contributes to the development of chronic symptoms. Veterans who sustained multiple TBIs experienced significantly higher rates of PTSD, depression, and suicidal thoughts and behaviors, than Veterans with a single or no history of TBI.[27] A history of repetitive TBIs has also been linked to CTE, diagnosed posthumously in Veterans.[28] Furthermore, one recent study showed that tau was elevated in military personnel and veterans who reported 3 or more TBIs in comparison to those who had sustained less than 3 TBIs.[10] This evidence suggests that repetitive TBIs may substantially increase the risk of negative psychological, behavioral, and neuronal deficits. Therefore, in this study we sought to examine the impact of repetitive mTBIs on both psychological symptoms and blood-based biomarkers.

To address the aforementioned research gaps, this study aimed to examine tau, Aβ40, Aβ42, and NFL concentrations in a cohort of military personnel and Veterans both with and without a history of mTBI. We predicted that concentrations of each of these proteins would be elevated in veterans with a history of TBI compared to those without a history of TBI. Furthermore, we conducted analyses to examine whether persistent symptoms of PTSD, PCS, and depression were associated with these biomarkers following a mTBI. Finally, in line with previous clinical research,[10] we examined the impact of repetitive TBIs (3 or more TBIs) versus sustaining 1–2 TBI(s) on protein concentrations.

Methods

Study Design

Military personnel and Veterans were enrolled at two sites, Fort Belvoir Community Hospital (FBCH, Virginia) and Walter Reed National Military Medical Center (WRNMMC, Bethesda, MD). This study is an ongoing recruitment and screening protocol and as such results presented represent an interim analysis. Exclusion criteria included psychosis, schizophrenia, schizoaffective disorder, and bipolar disorder, as well as contraindication to

MRI scanning (e.g., severe claustrophobia, residual shrapnel, or other MRI-incompatible metal). Participants completed a medical history and physical exam, a series of questionnaires, and collection of a blood sample. As part of the medical history and physical exam patient's height and weight were measured, which was used to calculate BMI. Current medications were also recorded. This study was approved by the Institutional Review Boards of the Uniformed Services University of the Health Science (USUHS), WRNMMC, and FBCH, and a witnessed written informed consent was obtained from each participant prior to data and sample collection.

Measures

TBI history was determined by the Ohio State University Traumatic Brain Injury Identification Method (OSU TBI-ID), which is a structured interview, conducted by research staff to assess lifetime TBI history.[29] This assessment includes incidences of LOC or AOC, number of injuries, cause of injuries, and age at each injury. A TBI was classified as an insult to the head that resulted in alteration in consciousness (AOC), and/or loss of consciousness (LOC) We identified three groups based on participants' TBI history: (1) repetitive TBIs (≥3); (2) 1–2 TBIs; (3) controls (no history of TBI). As part of the OSU assessment, participants also reported the length of time that they lost consciousness. We used this information to classify TBI severity into: Mild – AOC and/or LOC < 30 minutes; Moderate – LOC reported between 30 minutes – 24 hours; and Severe – LOC > 24 hours. Time since last injury (TSLI) was measured in years, as the difference between age at study visit and age at last TBI (classified as LOC/AOC).

PTSD symptoms were measured using the PTSD Checklist - Civilian Version (PCL-C).[30] This is a self-report measure with scores ranging from 17–85; higher scores indicate greater severity of PTSD symptoms. Symptoms can be broken into four clusters; intrusion, avoidance, negative mood, and hyperarousal. The PCL-C was derived from the PCL-Military version (PCL-M[31]) and is one of the most widely used self-report measures of PTSD.[32] Among Vietnam veterans the PCL-M had excellent test-retest reliability (r = .96) and excellent internal consistency (α = .97). The PCL has also been shown to have excellent sensitivity (.94), specificity (.86) and criterion validity (r = .93) with the Clinical Assessment of PTSD Scale (CAPS) which is considered the gold standard of PTSD diagnoses.[33]

Depression symptoms were measured using the patient health questionnaire (PHQ-9).[34] This is a self-report measure of depressive symptoms with scores ranging from 0–27, with higher scores indicating greater severity of symptoms. This PHQ-9 is also commonly used to assess depression in adults with TBIs and has good test-retest reliability (r = .76) and excellent sensitivity (.87) and good specificity (.78) when compared to the structured clinical interview for DSM disorders (SCID).[33]

Post-concussive symptoms were assessed using the Neurobehavioral Symptom Inventory (NSI).[35] The NSI is a 22-item assessment which can be broken down into four clusters somatosensory, affective, cognitive, and vestibular. The NSI is routinely used by large health care systems including the Department of Defense and Veteran Affairs to screen patients. The NSI has been shown to have excellent internal consistency (r = .95) and has been shown to be able to differentiate veterans with and without a history of TBI.[36]

The Combat Exposure Scale (CES) is a self-report measure containing 7 items that assess war zone-related stressors experienced by military personnel.[37] The total scores range from 0–41, with higher numbers indicating greater exposure to combat situations. Current medications were reported by participants. These were then classified in accordance to type (e.g. anti-depressant medications). These classifications were then dichotomized to indicate if participants were taking this medication or not. This resulted in three dichotomous (yes/no) categories; anti-depressant, anti-anxiety, and sleep medications. There was substantial overlap between participants taking anti-depressant and anti-anxiety medications. As such these categories were collapsed to form one variable; anti-depressants/anxiety medication.

Blood sampling and protein assays

Serum was processed and frozen at −80°C and stored until analyzed. Serum levels of tau, Aβ40, Aβ42, and NFL levels were measured in duplicate using Simoa™ a high-definition-1 analyzer, which is a paramagnetic bead-based enzyme-linked immunosorbent assay. The reported coefficient of variation (intra- and inter-plate) values were below 15% for all analytes.

Data Analysis

All data were analyzed using R statistical package (version 3.5). GraphPad Prism version 7.04 was used to produce graphs. Comparison of demographic, and clinical characteristics between the TBI and control group as well as comparisons across the three groups were conducted using Chi-square test (χ^2) and Mann-Whitney U and Kruskall Wallis-H tests. All continuous data are reported using the median (Med) and interquartile range (IQR). Logistic regression models were used to assess the difference in biomarkers between participants with a history of TBI and controls, covaried for age and sex. Partial correlation, covaried for age and sex, was used for assessing the relationship between the blood biomarkers and measures of injury severity, depression and post-traumatic stress symptoms.

Results

Demographics, military characteristics, and clinical measures of the 109 participants are described in Table 1. The sample was predominately male (85; 78%), and Caucasian (77; 70.6%). In this sample 94.1% of TBIs were classified as mild and 5.2% were classified as moderate. Two participants (0.7%) reported that they had sustained a severe TBI. The most recent TBI was a median of 5.0 years ago (IQR: 2.8–11.0), and 59.5% of the TBI group reported that they had been exposed to blasts. Of the remaining 40.5% of TBIs, 29.9% were a result of a motor vehicle accidents (MVA,) 26.5% were from a fall, 24.6% were from a direct blow (e.g. punch or struck by an object to the head) and 19% were sports related.

The TBI and control groups were similar with regard to sex and race, but the TBI group were slightly older (Med = 36 years; 38 years for the repetitive TBIs and 34 for the 1–2 TBIs group) than the control group (Med = 30 years). As such, age was controlled for in all group comparisons. Anti-depressant/anxiety medication use was significantly higher in the TBI group overall. In fact, 72% of participants within the repetitive TBI group reported taking

anti-depressants and/or anti-anxiety medication. Overall, the TBI group also had significantly greater combat exposure than the control group. Furthermore, the TBI group reported significantly worse symptoms on the PCL, NSI and the PHQ than the control group. Specifically, the repetitive TBI group had significantly poorer outcomes (indicated by higher scores) on all of the clinical symptoms measured (Table 1).

Biomarker differences between the TBI and control groups

Logistic regression models, controlling for age, sex, time since injury and anti-depressant/anxiety medication, were run to assess biomarker differences between (1) the TBI and control groups, and (2) 1–2 TBIs versus repetitive TBIs (TBIs ≥3) groups. There were no significant group differences between control and TBI groups for tau, Aβ40, Aβ42, or NFL concentrations (see Figure 1). For comparisons between the 1–2 TBIs and repetitive TBI groups there was a trend towards significance for NFL concentrations. Specifically, NFL was elevated in those who had sustained repetitive TBIs compared to those with 1–2 TBIs ($p = .07$; see Figure 1). There were no significant differences between the TBI groups in concentrations of tau, Aβ40, or Aβ42.

The Impact of PCL, NSI, and Depressive Symptoms on Biomarkers

Within the TBI group, we examined partial correlations, between each of the blood biomarkers and symptom reporting on the PCL (total score, and each of the four subscales), NSI (total score, and each of the four subscales), PHQ (total score); controlling for age, sex, time since injury and anti-depressant/anxiety medication. Tau was positively associated with the total scores for NSI ($p = .008$) and PHQ ($p = .01$; see Table 2). Tau was also significantly correlated with the subscales of NSI-somatosensory ($p < .001$), and PCL-negative mood ($p = .047$). NFL was significantly correlated with PCL-hyperarousal ($p = .017$). However, Aβ40 and Aβ42 were not significantly correlated with any of the symptoms measured (see Table 2).

Discussion

This study aimed to examine tau, Aβ40, Aβ42, and NFL in a young cohort of Veterans with and without a history of TBI. We found that there were no significant differences between TBI and control groups on any of the blood biomarkers concentrations measured, after controlling for age, sex, time since injury and anti-depressant/anxiety medication. However, when comparing participants with a history of TBI, NFL was trending towards having higher concentrations in those with repetitive TBIs versus participants who had only sustained 1–2 TBIs. Furthermore, within the TBI group, tau concentrations were significantly correlated with greater symptom severity on the NSI, PCL and PHQ, and NFL concentrations were positively correlated with PCL-hyperarousal symptoms, irrespective of age, gender, time since injury and anti-depressant/anxiety medication. These findings indicate that tau and NFL may play a role in the maintenance of neurological and behavioral symptoms following TBI.

In this study, higher tau concentrations were associated with higher total NSI scores and more NSI-somatosensory, PCL-negative mood symptoms, and higher PHQ scores.

Symptoms such as increased sensitivity to visual and auditory stimuli, as recorded in the NSI-somatosensory subscale, are routinely reported in clinical settings following a TBI.[35,38–40] Similarly, patients with PTSD commonly report a higher sensitivity to sensory stimuli, describing the sensation of being bothered or overwhelmed by such input.[40,41] Even though these symptoms have been thoroughly characterized, the mechanisms underlying the sensory abnormalities linked to TBI and PTSD are poorly understood. From a neurocircuitry point of view, evidence points towards mechanisms involving increased activity at earlier stages of sensory processing and reduced top-down modulation in both pathologies.[39,41,42] In TBI, activity changes in large neural networks involving frontal and temporal regions, as well as structural changes in regions such as the hippocampus, including tau accumulation, have been reported and associated with disruptions in high level cognitive functions.[39,42–44] Animal studies have shown that TBI induces long-term neuronal hyperexcitability in the sensory cortex.[39,45] PTSD is commonly associated with alterations in areas of the frontal cortex, hippocampus, amygdala, and overall reductions in neuronal volume.[46–48] In addition, the amygdala, which is dysfunctional in PTSD, influences sensory processing through projections to neuromodulatory centers from the forebrain and brainstem, which guide attention, mood and adjust sensory responses to the demands of the environment and internal state of the individual.[49] Therefore, we hypothesize that tau neurotoxicity affects sensory processing and modulation, which relates to NSI-somatosensory and alteration of mood (PCL-negative mood and PHQ total score). Subsequent investigations should explore changes in sensory processing and its relationship to TBI and PTSD symptoms and underlying pathology.

In this study, we also observed that NFL concentrations were slightly increased in the blood of military personnel with 3 or more TBIs in comparison to those with 1–2 TBIs. NFL concentrations are hypothesized to reflect axonal loss and damage, suggesting that axonal injury may relate to this finding.[23,24] Previous studies have also suggested an association between NFL and repetitive TBIs. In one study, increased CSF NFL levels were observed in hockey players who had repeated TBIs with concurrent PCS.[24] Moreover, elevated CSF NFL levels have been associated with both acute and recurrent head trauma in amateur boxers.[50] Elevated levels of NFL in peripheral blood has also been detected in American football college athletes over the course of a season, even in those who did not sustain a diagnosed concussion.[51] Elevations in NFL concentrations were also noted within the first 24 hours, post-injury, of severe TBI patients[26] and have been shown to increase during the first 1–2 weeks following moderate to severe TBIs,[23] however, understanding of long-term patterns of NFL following injury have not been determined. Different mechanisms likely account for the NFL increase at different timepoints post-TBI. At acute timepoints, elevated NFL levels are linked to the primary injury as well as early TBI-induced pathological processes.[23] In patients with chronic TBIs, as in this cohort, elevated NFL levels likely reflect secondary pathological processes.[23,52] Importantly, the half-life of NFL *in vivo* is approximately three weeks.[53] Thus, the elevated NFL levels observed in this study may reflect an ongoing process of axonal degeneration due to lasting TBI-induced pathological processes. However, there is a need for additional studies, potentially with larger sample sizes of personnel with a history of TBI, to better understand NFL changes and potentially link these changes to neuroimaging following TBIs in military personnel.

We also found a significant and negative association between NFL and PCL-hyperarousal symptoms in participants with a history of TBI, even after controlling for age, gender, time since injury and anti-depressant/anxiety medication use. This suggests that lower NFL concentrations are associated with higher hyperarousal symptoms. We did not however, observe an association between blood NFL levels and occurrence of PCS, or depressive symptoms. Taken together these results are surprising given that previous studies have established a relationship between NFL levels, functional outcomes, and TBI-induced symptoms. Specifically, one study of patients with severe TBIs, found that levels of NFL in both blood (serum) and CSF were significantly correlated to global outcome, measured using the Glasgow Outcome Scale.[23] In less severely injured subjects, CSF NFL levels in hockey players with concussions, or mild TBIs, with PCS that lasted more than a year were elevated when compared to players with PCS that lasted less than a year, as well as healthy controls.[24] Therefore, these findings suggest that elevated levels of NFL in those with repetitive injuries may play a role in more long-term outcomes, and that additional studies are warranted to better understand the possible implications of these elevations.

This study has a number of limitations, including the lack of neuroimaging and neuropsychological data, the study sample being predominantly male, and the assessment at a single time point using retrospective self-report measures which cannot be objectively validated. These limitations preclude us from definitively establishing causation with regard to the TBI, elevations in tau and NFL as well as symptoms. Longitudinal research addressing these limitations is needed to provide further information about the trajectories of symptom severity and tau and NFL concentrations over time. Future studies would also benefit from including other sources of variation in both these proteins and neuropsychological outcomes, such as genetic predisposition, physical activity and other lifestyle variables. However, our findings indicate that tau and NFL may be important candidate biomarkers that potentially play a role in maintenance of psychological symptoms in those who have experienced TBI, and particularly following repetitive TBIs. The present study shows the utility of measuring biomarkers chronically post-injury. There is a critical need for studies of biomarkers longitudinally following TBI to understand the high degree of variability in recovery from TBI, to identify those military personnel and veterans most at risk for chronic symptoms.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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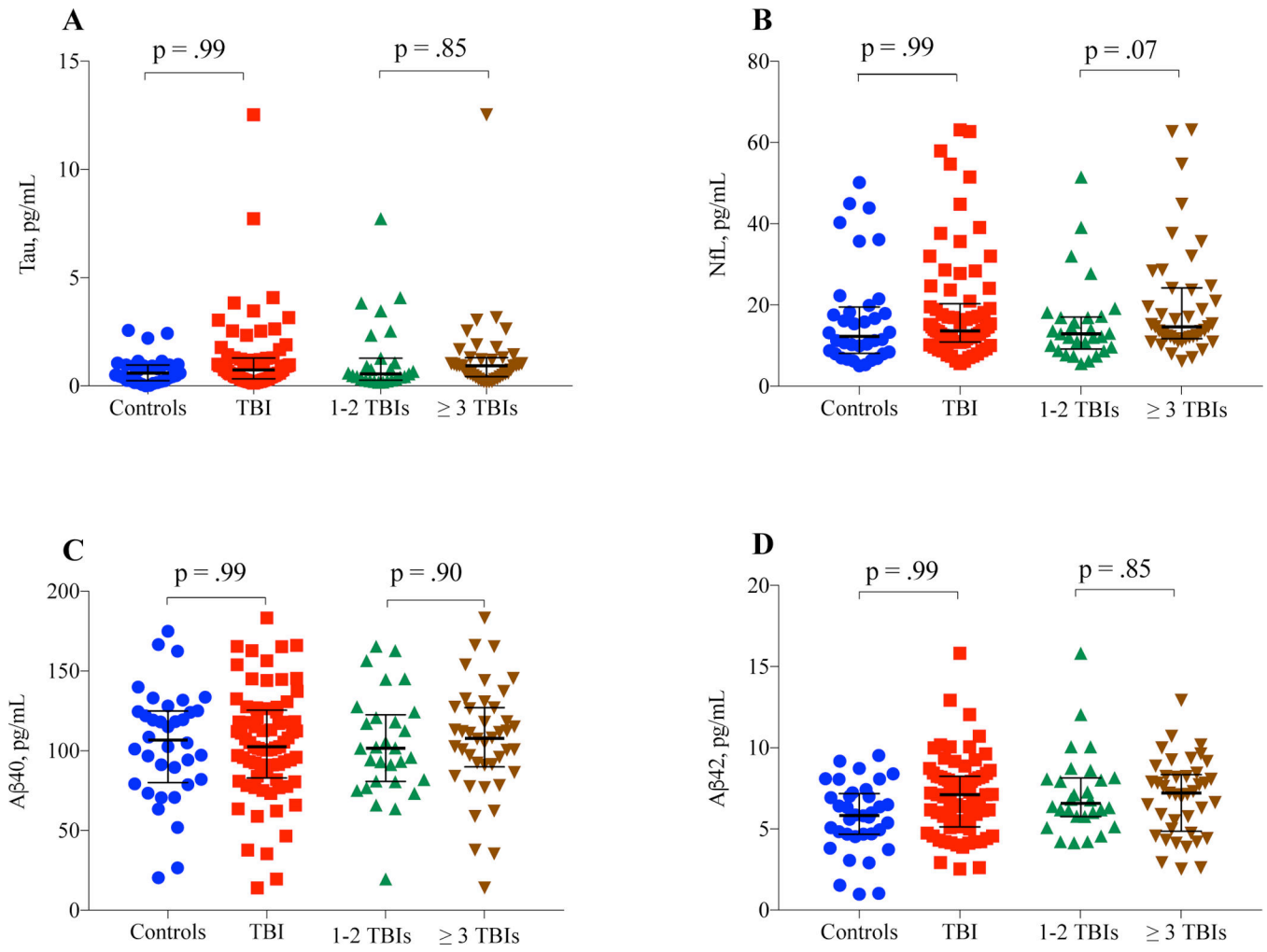

Figure 1.

The results of logistic regression, controlling for age, sex, time since injury, and anti-depressant/anxiety medication. The differences between (1) TBI and controls and (2) 1–2 TBIs and repetitive TBIs, on the 4 concentrations are shown in A. tau; B. Aβ40; C. Aβ42; and D. NFL.

Table 1.

Demographic, military and clinical characteristics

		TBI		p[a]	p[b]
	Controls (n = 35)	1–2 TBIs (n=30)	≥3 TBIs (n = 44)		
Age, years; Median (IQR)	30.0 (23.0–40.0)	34 (31–45)	37.5 (32–49.75)	.001	.002
Sex, Male; no. (%)	28 (80.0)	22 (73.3)	35 (79.5)	.727	.770
Race; no. (%)				.853	.810
White	26 (74.3)	20 (66.7)	31 (70.5)		
Black or African-American	4 (11.4)	6 (20.0)	8 (18.2)		
Other/unknown	5 (14.3)	4 (13.3)	5 (11.4)		
BMI; Median (IQR)	28.2 (23.7–29.7)	27.8 (24.9–30.5)	28 (24.6–30.8)	.548	.835
Anti-depressants and or anti-anxiety yes; no. (%)	2 (5.7)	13 (43.3)	32 (72.7)	<.001	<.001
Sleep medications, yes; no. (%)	2 (5.7)	3 (10.0)	9 (20.5)	.126	.130
Anti-psychotics, yes; no. (%)	-	2 (6.7)	2 (4.5)	.161	.334
Military Status; no. (%)				.412	.365
Active Duty Military	29 (82.9)	20 (66.7)	29 (65.9)		
Reserve Component	1 (2.9)	2 (6.7)	-		
National Guard	-	1 (3.3)	1 (2.3)		
Retired from Military	4 (11.4)	6 (20.0)	9 (20.5)		
Veteran	1 (2.9)	1 (3.3)	5 (11.4)		
TSLI years; Median (IQR)	-	11 (3.75–18.25)	5.0 (2.0–6.75)	<.001	<.001
Combat Exposure; Median (IQR)	1.5 (0 – 3)	15 (4–23)	23.5 (9.5–35.3)	<.001	<.001
Clinical Symptoms					
NSI; Median (IQR)	1.0 (0–3)	13.5 (2–48)	46 (30.3–55.5)	< .001	<.001
PCL; Median (IQR)	17 (17–18)	35 (17–60.5)	56 (50.3–65)	< .001	<.001
PHQ; Median (IQR)	0 (0–0)	3 (0–14.3)	14.5 (10.3–19.0)	< .001	<.001

Note: IQR – Interquartile Range; NSI – Neurobehavioral Symptom Inventory; PCL – PTSD Checklist; PHQ – Patient Health Questionnaire; TSLI – Time since last injury.

[a]This p-value represents the significance of group comparisons between Controls (n = 35) and TBI (n = 74) groups

[b]This p-value represents the significance of group comparisons between Controls (n = 35), 1–2 TBIs (n = 30), and the repetitive TBI (n = 44) groups

Table 2.

Partial correlations between blood biomarker concentrations and psychometric measures within patients who had a history of TBI.

Psychometric measures	Tau		NFL		Aβ40		Aβ42	
	ρ	*p*	ρ	*p*	ρ	*p*	ρ	*p*
NSI, total	.33	**.008**	−.33	.83	.002	.99	.16	.21
NSI, somatosensory	.43	**.0004**	.06	.66	.04	.74	.17	.20
NSI, affective	.24	.06	−.14	.28	−.08	.53	.13	.33
NSI, vestibular	.21	.09	−.08	.51	−.02	.90	.05	.72
NSI, cognitive	.22	.09	−.08	.49	−.15	.23	.02	.87
PCL, total	.22	.09	−.17	.17	.03	.80	.18	.17
PCL, Intrusion	.22	.09	−.04	.75	.05	.71	.14	.27
PCL, avoidance	.19	.14	−.23	.08	.11	.38	.07	.54
PCL, negative mood	.25	**.047**	−.07	.60	−.09	.46	-.16	.20
PCL, hyperarousal	.08	.52	−.30	**.017**	.006	.96	-.06	.65
PHQ-9	.32	**.01**	−.16	.20	−.06	.66	.13	.32

Abbreviations: NFL - neurofilament light; Aβ40 - Amyloid-β-40; Aβ42 - Amyloid-β-42; NSI - Neurobehavioral Symptom Inventory; PCL - PTSD Check List; PHQ-9 - Patient Health Questionnaire. The results show the partial correlation coefficient, controlling for age, sex, time since injury, and anti-depressant/anxiety medication.