Peripheral Total Tau in Military Personnel Who Sustain Traumatic Brain Injuries During Deployment

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**IMPORTANCE** Approximately one-third of military personnel who deploy for combat operations sustain 1 or more traumatic brain injuries (TBIs), which increases the risk for chronic symptoms of postconcussive disorder, posttraumatic stress disorder, and depression and for the development of chronic traumatic encephalopathy. Elevated concentrations of tau are observed in blood shortly following a TBI, but, to our knowledge, the role of tau elevations in blood in the onset and maintenance of chronic symptoms after TBI has not been investigated.

**OBJECTIVES** To assess peripheral tau levels in military personnel exposed to TBI and to examine the relationship between chronic neurological symptoms and tau elevations.

**DESIGN, SETTING, AND PARTICIPANTS** Observational assessment from September 2012 to August 2014 of US military personnel at the Madigan Army Medical Center who had been deployed within the previous 18 months. Plasma total tau concentrations were measured using a novel ultrasensitive single-molecule enzyme-linked immunosorbent assay. Classification of participants with and without self-reported TBI was made using the Warrior Administered Retrospective Casualty Assessment Tool. Self-reported symptoms of postconcussive disorder, posttraumatic stress disorder, and depression were determined by the Neurobehavioral Symptom Inventory, the Posttraumatic Stress Disorder Checklist Military Version, and the Quick Inventory of Depressive Symptomatology, respectively. Group differences in tau concentrations were determined through analysis of variance models, and area under the receiver operating characteristic curve determined the sensitivity and specificity of tau concentrations in predicting TBI and chronic symptoms. Seventy participants with self-reported TBI on the Warrior Administered Retrospective Casualty Assessment Tool and 28 control participants with no TBI exposure were included.

**MAIN OUTCOMES AND MEASURES** Concentration of total tau in peripheral blood.

**RESULTS** Concentrations of plasma tau were significantly elevated in the 70 participants with self-reported TBI compared with the 28 controls (mean [SD], 1.13 [0.78] vs 0.63 [0.48] pg/mL, respectively; F<sub>1,97</sub> = 4.97; P = .03). Within the self-reported TBI cases, plasma total tau concentrations were significantly associated with having a medical record of TBI compared with self-reported TBI only (mean [SD], 1.57 [0.92] vs 0.85 [0.52] pg/mL, respectively; F<sub>1,69</sub> = 6.15; P = .02) as well as reporting the occurrence of 3 or more TBIs during deployment compared with fewer than 3 TBIs (mean [SD], 1.52 [0.82] vs 0.82 [0.60] pg/mL, respectively; F<sub>1,69</sub> = 8.57; P = .008). The severity of total postconcussive symptoms correlated with total tau concentrations in the self-reported TBI group (r = 0.37; P = .003).

**CONCLUSIONS AND RELEVANCE** Military personnel who report multiple TBIs have long-term elevations in total tau concentration. The total tau concentration relates to symptoms of postconcussive disorder.
Peripheral Tau in Military Personnel With Traumatic Brain Injuries

Traumatic brain injury (TBI) is recognized as the signature injury in military personnel deployed for combat operations in Operation Enduring Freedom and Operation Iraqi Freedom. Combat injuries and injuries in nondeployed settings have resulted in more than 300,000 TBI cases, with many experiencing multiple TBIs. While most of these TBIs are mild and individuals show good recovery, TBIs place military personnel at risk for chronic neurological and psychological symptoms, including postconcussive disorder (PCD), posttraumatic stress disorder (PTSD), and depression, and for the development of chronic traumatic encephalopathy.2-6

Current diagnostic tools are unable to identify individuals at greatest risk for chronic neurological deficits following TBI. Repeated TBIs are linked to neuronal structural and functional damage and the effects can take time to manifest. Furthermore, chronic PCD overlaps with psychiatric disorders commonly reported in military personnel including PTSD and depression,7 presenting challenges for clinical management. Cognitive therapy can be effective in treating these comorbid symptoms, but additional methods are needed to mitigate the risk for progressive cognitive declines. Diagnostic and prognostic biomarkers will likely be required to develop therapeutic strategies to mitigate these risks.

Secondary injury processes, including inflammation, that persist for months or years likely contribute to neuronal loss, functional impairments, and changes in neuroplasticity and ultimately promote chronic symptoms; however, biomarkers of chronic symptoms following TBI are not well described. Elevated concentrations of tau in cerebral spinal fluid9 and in blood shortly following TBI have been reported10,11 and may relate to tau accumulations in neurons and glial cells, which are the pathologic hallmarks of chronic traumatic encephalopathy. Chronic traumatic encephalopathy and other neurodegenerative conditions have been linked to TBI and specifically multiple TBIs,12,13 suggesting that there may be shared mechanisms related to total tau accumulation in neurons that can initiate neurofibrillary tangles and result in cognitive decline.14 To our knowledge, studies that examine the role of tau accumulations in the onset and maintenance of chronic symptoms after TBI have not been reported, leading us and others to question whether tau elevations relate to chronic symptoms in military personnel who sustain TBI.

Tau is a microtubule-associated protein that functions as a structural element in the axonal cytoskeleton. Elevations of tau concentration are an indication of axonal injury and are observed in the cerebral spinal fluid and peripheral blood of patients with severe TBI, professional boxers, and concussed athletes.9-11 Peripheral tau levels can remain elevated for hours to days and return to levels comparable to those in controls within a few days to months following injury.9 Therefore, current studies link TBI and concussion to short-term tau elevations; however, to our knowledge, the relationship of tau in the onset of chronic symptoms has not been investigated. A primary reason for a limited understanding of the role of tau in chronic TBI symptoms is the very low concentration in peripheral blood, making it difficult to measure. The recent development of an ultrasensitive immunoassay technology, the single-molecule immunoarray (Simoa) technology developed by Quanterix, Inc,15 now provides a sensitivity that is approximately 1000 times improved compared with the conventional assays in tau detection, making it feasible to study the relationship between tau concentrations in blood and chronic TBI symptoms.

In this study, we examine the associations between tau concentrations using the Simoa system and the occurrence, severity, number, and frequency of deployment-related TBIs. We also examine the relationship between chronic neurological symptoms and tau elevations, while considering the impact of psychological symptoms of PTSD and depression. By combining this novel assay to determine tau concentrations along with TBI histories and related symptoms, we provide evidence for a potential role of tau in chronic TBI symptoms.

Methods

This study was an observational assessment from September 2012 to August 2014 of US military personnel at the Madigan Army Medical Center who had been deployed within the previous 18 months. Exclusion criteria included the following: (1) history of drug or alcohol abuse in the previous year; (2) current severe medical condition that required long-term treatments (eg, cancer, diabetes mellitus, human immunodeficiency virus, autoimmune disorders) or a severe psychiatric condition (ie, schizophrenia or bipolar disorder); and (3) severe neurological disorders (eg, multiple sclerosis, seizure disorders, history of stroke). This study was approved by the Madigan Army Medical Center Institutional Review Board, and written informed consent was obtained from each individual prior to any baseline measurements.

Determination of TBI

To be classified as a self-reported TBI case, the participant reported a history of TBI based on the Warrior Administered Retrospective Casualty Assessment Tool and endorsed either losing consciousness or experiencing symptoms of posttraumatic amnesia.16 Diagnosis of or treatment for TBI was extracted from medical records in accordance with the American Congress of Rehabilitation Medicine mild TBI criteria.

Controls met the same inclusion and exclusion criteria as cases with the exception of TBI, which was determined by the Warrior Administered Retrospective Casualty Assessment Tool including no self-report of lifetime TBIs as well as no history of TBI in their medical record.

Determination of PCD, PTSD, and Depression Symptoms

The 22-item Neurobehavioral Symptom Inventory (NSI) was administered by trained research assistants to measure postconcussive symptom severity. It rates the presence or severity of each symptom on a 5-point scale, with higher scores indicating greater severity of symptoms. It has high internal consistency (total α = .95; subscale α = .88-.92) and reliability (r = 0.88-0.93).17 Symptoms of PTSD were assessed by the

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**Table 1. Demographic and Clinical Characteristics for the Group With No TBI, Those With a Medical Record of TBI, and Those With Self-reported TBI Only**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No TBI (n = 28)</th>
<th>Medical Record of TBI (n = 24)</th>
<th>Self-reported TBI Only (n = 46)</th>
<th>Significance</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>28.40 (4.47)</td>
<td>30.25 (5.61)</td>
<td>30.39 (4.58)</td>
<td>F&lt;sub&gt;2,96&lt;/sub&gt; = 1.59</td>
<td>.21</td>
</tr>
<tr>
<td>Male, No. (%)</td>
<td>27 (96.4)</td>
<td>24 (100.0)</td>
<td>45 (97.8)</td>
<td>χ² = 0.832</td>
<td>.66</td>
</tr>
<tr>
<td>Race, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>18 (64.3)</td>
<td>21 (87.5)</td>
<td>42 (91.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>3 (10.7)</td>
<td>1 (4.2)</td>
<td>1 (2.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Native American or Hawaiian</td>
<td>2 (7.1)</td>
<td>1 (4.2)</td>
<td>1 (2.1)</td>
<td>χ² = 8.379</td>
<td>.16</td>
</tr>
<tr>
<td>Asian</td>
<td>3 (10.7)</td>
<td>1 (4.2)</td>
<td>1 (2.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other or unknown</td>
<td>2 (7.1)</td>
<td>0</td>
<td>1 (2.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marital status, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>22 (78.6)</td>
<td>21 (87.5)</td>
<td>42 (91.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never been married</td>
<td>4 (14.3)</td>
<td>2 (8.3)</td>
<td>0</td>
<td>χ² = 7.893</td>
<td>.25</td>
</tr>
<tr>
<td>Separated or divorced</td>
<td>1 (35.7)</td>
<td>1 (4.2)</td>
<td>4 (8.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Education level, mean (SD), y</td>
<td>12.88 (2.54)</td>
<td>13.15 (2.97)</td>
<td>13.02 (3.70)</td>
<td>F&lt;sub&gt;2,96&lt;/sub&gt; = 1.13</td>
<td>.49</td>
</tr>
<tr>
<td>Time since most recent deployment, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;6 mo</td>
<td>9 (32.1)</td>
<td>4 (16.7)</td>
<td>2 (4.3)</td>
<td>χ² = 27.176</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>6-12 mo</td>
<td>7 (25.0)</td>
<td>19 (79.2)</td>
<td>22 (47.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;12 mo</td>
<td>12 (42.9)</td>
<td>1 (4.2)</td>
<td>22 (47.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deployed to OEF, No. (%)</td>
<td>28 (100.0)</td>
<td>24 (100.0)</td>
<td>46 (100.0)</td>
<td>χ² = 0.00</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Deployed to OIF, No. (%)</td>
<td>14 (50.0)</td>
<td>19 (79.2)</td>
<td>7 (15.2)</td>
<td>χ² = 28.356</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>PCL-M score for PTSD, mean (SD)</td>
<td>16.9 (12.1)</td>
<td>34.8 (17.2)</td>
<td>38.9 (19.8)</td>
<td>F&lt;sub&gt;2,96&lt;/sub&gt; = 7.3</td>
<td>.01</td>
</tr>
<tr>
<td>QIDS score for depression, mean (SD)</td>
<td>8.7 (4.8)</td>
<td>11.4 (7.3)</td>
<td>14.7 (8.0)</td>
<td>F&lt;sub&gt;2,96&lt;/sub&gt; = 3.3</td>
<td>.02</td>
</tr>
</tbody>
</table>

**PTSD Checklist Military Version**, with higher numbers indicating greater severity.18,19 The Quick Inventory of Depressive Symptomatology was used to measure total symptoms of depression, with higher scores indicating greater severity.19

**Biological Samples**
Nonfasting blood samples were collected into plastic dipotassium EDTA tubes, inverted 5 times, placed on ice, and centrifuged (15 minutes, 2000g, 4°C), and plasma was aliquoted. Owing to variability in participant availability, collection times ranged from 9 AM to 4 PM (mean, 11:36 AM [SD, 1 hour 54 minutes]); however, the groups did not significantly differ in the time of collection. All samples were processed, including centrifuging, within 30 minutes of the blood draw and then stored at −80°C until sufficient samples had been collected to complete a batch assay.

**Biochemical Procedures**
Tau concentrations in plasma samples were measured with a digital array technology (Simoa; Quanterix Corporation), which uses a single-molecule enzyme-linked immunoarray (Simoa) method previously described.20 The Simoa Human Total Tau assay uses a combination of a monoclonal capture antibody that reacts with a linear epitope in the midregion of all tau isoforms, and a detection antibody that reacts with a linear epitope in the N-terminus of total tau. The laboratory scientists who undertook the analyses were blinded to the participant groups, and there was no difference in the distribution of cases and controls in the plates. All assays were run in duplicate during a 3-day period for a total of 4 plates. Both the intra-assay and interassay coefficients were below 20%, with average coefficients of variation of 4.5% and 7.23%, respectively. The limit of detection for the assay is 0.012 pg/mL.

**Statistical Analysis**
Descriptive statistics for all demographic and clinical variables were calculated using SPSS Statistics version 22.0 software (IBM SPSS Inc) (Table 1 and Table 2). Comparisons were made between the groups using χ² test for categorical variables and analysis of variance as well as adjustment for covariates. P < .05 was considered statistically significant after adjustment for the high number of multiple comparisons using Bonferroni correction. The area under the receiver operating characteristic curve (AUC) was determined for total tau concentrations, comparing the following: (1) military personnel with a self-reported TBI vs controls with no TBI; (2) military personnel with a clinical diagnosis of TBI vs those with self-reported TBI only; and (3) military personnel who reported 3 or more TBIs vs fewer than 3 TBIs during deployment. A logistic regression model was used to determine which of these 3 variables was most related to having a tau concentration that was in the top quartile of values in the sample and to determine whether PCD symp-
toms related to tau elevations, independent of PTSD and depression symptoms. The forced entry method was used for this model, and odds ratios were generated for each variable that included PTSD and depression diagnoses. Lastly, the Spearman rank correlation coefficient was used to determine correlations of total tau concentrations with PCD symptoms and with injury characteristics.21

Results

Demographic and Clinical Characteristics

The demographic and clinical characteristics of the 98 participants used in this analysis are described in Table 1. The self-reported TBI group (n = 70) was matched to a control group (n = 28) of recently deployed service members who did not experience TBI but had similar demographic characteristics (age, sex, or race) as well as deployment factors including the time since deployment and the number of deployments. In the TBI group, approximately 2 had a medical record of a skull fracture and none had spinal cord injuries. The sample was primarily male and white and demonstrated high rates of comorbid symptoms of depression and PTSD. The mean (SD) ages of the self-reported TBI and control groups were 30.39 (4.58) and 28.40 (4.47) years, respectively. The control group deployed more recently compared with the self-reported TBI group (χ2 = 27.176; P < .001).

In the self-reported TBI group, 24 participants (34.3%) had a medical record of TBI (Table 3). The mean (SD) number of brain injuries reported was 3.0 (2.5), and 21 participants (30.0%) reported 4 or more TBIs. The most common types of injuries were a blow to the head, blast exposure, vehicular collision, and sports-related TBI. Seventeen participants (23.6%) had 1 or more TBIs prior to deployment. Seven participants (10.0%) reported losing consciousness for more than 20 minutes, and 37 (52.9%) lost consciousness for between 1 and 20 minutes. Time since last TBI ranged from 3 months to more than 3 years, with most participants reporting the TBI at least 18 months prior to the study.

The self-reported TBI group (n = 70) reported a greater overall severity of postconcussive symptoms compared with controls (n = 28) (F1,97 = 23.26; P = .001) (Table 2). Neurobehavioral Symptom Inventory scores on 10 of the 22 components were significantly different between the 2 groups based on a P value of .05, which was then adjusted for multiple comparisons.

Relation of TBI to Tau Concentrations in Group Comparisons

In our first comparison, a significantly elevated concentration of total tau was found in the self-reported TBI group...
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Table 3. Characteristics of TBI in Military Personnel

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Military personnel with TBI, No.</td>
<td>70</td>
</tr>
<tr>
<td>TBIs, No.</td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>3.0 (2.5)</td>
</tr>
<tr>
<td>1</td>
<td>31 (44.3)</td>
</tr>
<tr>
<td>2-3</td>
<td>18 (25.7)</td>
</tr>
<tr>
<td>4-6</td>
<td>12 (17.1)</td>
</tr>
<tr>
<td>&gt;6</td>
<td>9 (12.9)</td>
</tr>
<tr>
<td>Acute severity</td>
<td></td>
</tr>
<tr>
<td>Loss of consciousness, min</td>
<td></td>
</tr>
<tr>
<td>1-20</td>
<td>37 (52.9)</td>
</tr>
<tr>
<td>&gt;20</td>
<td>7 (10.0)</td>
</tr>
<tr>
<td>Symptoms of concussion</td>
<td>51 (72.9)</td>
</tr>
<tr>
<td>Time since last TBI, mo</td>
<td></td>
</tr>
<tr>
<td>3-6</td>
<td>4 (5.7)</td>
</tr>
<tr>
<td>6-12</td>
<td>6 (8.6)</td>
</tr>
<tr>
<td>18-24</td>
<td>22 (31.4)</td>
</tr>
<tr>
<td>24-36</td>
<td>20 (28.6)</td>
</tr>
<tr>
<td>&gt;36</td>
<td>18 (25.7)</td>
</tr>
<tr>
<td>Medical record of TBI</td>
<td>24 (34.3)</td>
</tr>
<tr>
<td>Injury type</td>
<td></td>
</tr>
<tr>
<td>Blast</td>
<td>31 (44.3)</td>
</tr>
<tr>
<td>Blow to head</td>
<td>47 (67.1)</td>
</tr>
<tr>
<td>Fall</td>
<td>5 (7.1)</td>
</tr>
<tr>
<td>Vehicular collision</td>
<td>12 (17.1)</td>
</tr>
<tr>
<td>Sports</td>
<td>11 (15.7)</td>
</tr>
<tr>
<td>Report of TBI prior to deployment</td>
<td>17 (23.6)</td>
</tr>
</tbody>
</table>

Abbreviation: TBI, traumatic brain injury.

Figure 1. Plasma Total Tau Concentration

A. Plasma total tau concentration was higher in military personnel with self-reported traumatic brain injury (TBI) compared with control samples ($F_{1,97} = 4.97; P = .03$). B. Plasma total tau concentration was higher in the group with a medical record of TBI compared with those with self-reported TBI only ($F_{1,69} = 6.15; P = .02$). C. Plasma total tau concentration was associated with the number of TBIs ($F_{1,69} = 8.57; P = .008$). Horizontal lines indicate means.

In the top 25% of the sample (odds ratio = 5.33; 95% CI, 3.04-6.98; $P = .02$).

(n = 70) compared with the control group (n = 28) (mean [SD], 1.13 [0.78] vs 0.63 [0.48] pg/mL, respectively; $F_{1,97} = 4.97; P = .03$) (Figure 1). Within the self-reported TBI group, several variables were significantly related to total tau concentrations. Having a medically recorded TBI (n = 24) was associated with elevations in total tau concentration compared with those with self-reported TBI only (n = 46) (mean [SD], 1.57 [0.92] vs 0.85 [0.52] pg/mL, respectively; $F_{1,69} = 6.15; P = .02$) (Figure 1). Military personnel with 3 or more TBIs (n = 28) had a significant elevation of total tau compared with those who had fewer than 3 reported TBIs (n = 42) (mean [SD], 1.52 [0.82] vs 0.82 [0.60] pg/mL, respectively; $F_{1,69} = 8.57; P = .008$) (Figure 1). The time since last TBI was not significant, nor was having a TBI in the previous year. Having lost consciousness for more than 20 minutes or between 1 and 20 minutes was not significant, which may be a result of these groups having fewer than 10 participants.

Receiver operating characteristic analyses showed modest accuracy of plasma tau for the identification of self-reported TBI (AUC = 0.74; 95% CI, 0.61-0.86; $P = .007$), a medically documented TBI (AUC = 0.69; 95% CI, 0.51-0.89; $P = .007$), and a report of 3 or more TBIs (AUC = 0.73; 95% CI, 0.61-0.86; $P = .003$) (Figure 2). In a logistic regression model that included these 3 TBI characteristics, only reporting 3 or more TBIs was related to having a tau concentration...
Impact of Symptoms of PCD, PTSD, and Depression on Total Tau Concentrations

For the 2 PCD outcome measures (total score and symptom clusters), all were significantly associated with tau levels. The severity of total postconcussive symptoms correlated with total tau concentrations in the self-reported TBI group ($r = 0.37; P = .003$) (Figure 2). In the self-reported TBI group, total tau concentrations significantly correlated with postconcussive symptoms within the factor categories of vestibular ($r = 0.29; P = .03$), somatic ($r = 0.31; P = .02$), cognitive ($r = 0.28; P = .02$), and emotional/affective ($r = 0.24; P = .02$).

In the entire sample of participants, PTSD symptoms correlated with total tau concentrations ($r = 0.21; P = .04$) but depression severity did not ($P = .14$). In a regression model that included PCD symptoms, the relationship between total tau concentrations and PTSD was no longer significant ($P = .05$), suggesting that PCD symptoms are most related to tau elevations, even when PTSD is controlled. In the entire sample, we observed a high correlation between PTSD and PCD symptoms ($r = 0.71; P = .004$). To determine whether the relationship between tau elevations and postconcussive symptoms was independent of both PTSD and depression severity, a logistic regression model including PCD symptoms within the top third of the sample (Neurobehavioral Symptom Inventory score $\geq 48$) as well as PTSD (PTSD Checklist Military Version score $\geq 50$) and depression (Quick Inventory of Depressive Symptomatology score $\geq 13$) diagnoses was undertaken. The result was an odds ratio of 4.22 (95% CI, 1.89-8.02; $P = .04$) of having a tau concentration in the top quartile in participants with PCD symptoms in the top third of the sample, which controlled for the impact of PTSD and depression severity.

Discussion

Military personnel who sustain 1 or multiple TBIs sometimes report chronic neurological and psychological symptoms that can significantly impact their health and well-being. The complex and multifactorial nature of these comorbidities presents a substantial challenge for the treatment of TBI-related symptoms. Biological markers that are sensitive and specific to persistent TBI-related symptoms have not been identified. For the first time, to our knowledge, we report that tau concentration is elevated in peripheral blood of military personnel with a history of TBI, specifically in military personnel with a medical diagnosis of TBI or those who report more than 3 TBIs during deployment. We also link chronic symptoms of PCD to tau elevations, independent of PTSD and depressive symptoms.

Previous studies illustrate how tau concentrations increase in the peripheral blood shortly after a TBI and return to baseline concentrations within 6 months. Using Simoa technology with an earlier version of the total tau assay, total tau elevations following concussion in hockey players correlated with PCD symptom resolution at 6 days following injury, suggesting that long-term tau elevation may contribute to postacute neurological symptoms. Herein, we report that total tau concentrations are increased in military personnel who sustain TBIs during deployment and correlate to chronic PCD symptoms that are present months to years after their injuries. These findings suggest that months to years after the primary brain injury, there may be a continuation of secondary injuries with residual axonal degeneration and blood-brain barrier disruptions in this population that may contribute to the maintenance of PCD.

Figure 2. Specificity of Tau in Traumatic Brain Injuries (TBIs) and Associated Chronic Postconcussive Disorder Symptoms

A, Receiver operating characteristic analyses showed modest accuracy of plasma tau concentration for the identification of self-report of TBI (area under the receiver operating characteristic curve = 0.74; 95% CI, 0.61-0.86; $P = .007$), a medically documented TBI (area under the receiver operating characteristic curve = 0.69; 95% CI, 0.51-0.89; $P = .007$), and a report of 3 or more TBIs (area under the receiver operating characteristic curve = 0.73; 95% CI, 0.61-0.86; $P = .003$). B, Plasma total tau concentration is associated with Neurobehavioral Symptom Inventory (NSI) score for chronic postconcussive disorder symptoms ($r = 0.37; P = .003$).

![Figure 2](image-url)
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Original Investigation Research

TBI as well as multiple TBIs, which limits our ability to determine whether these tau elevations are a result of neural damage from TBI or of other sources including muscle. In addition, the study includes only 1 time, making it impossible to study the temporal profile of tau elevations and impact on recovery. There is also a good deal of variation in tau concentration in both groups that cannot be attributed to our information on TBI alone. Future studies would need to examine additional sources of variation such as genetic predisposition, activity level, and additional information regarding TBIs, including a better approximation of the severity of the TBIs sustained. Ultimately, studies that provide a direct mechanistic relationship between TBIs and tau aggregation could support the use of therapeutics such as direct delivery of proteasomes for reducing tau aggregates. This would be invaluable considering the dearth of treatments for TBIs and chronic PCD symptoms.

Conclusions

Our findings of increases in total tau concentration in the peripheral blood in military personnel with multiple TBIs and chronic PCD symptoms suggest that tau accumulations may contribute to chronic neurological symptoms following TBI.

ARTICLE INFORMATION

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