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Plasma Tau and Amyloid Are Not Reliably Related to Injury Characteristics, Neuropsychological Performance, or White Matter Integrity in Service Members with a History of Traumatic Brain Injury

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Abstract

The aim of this study was to examine the relationship between plasma tau and amyloid beta-42 (Aβ42), neuropsychological functioning, and white matter integrity in U.S. military service members with ($n = 155$) and without ($n = 42$) a history of uncomplicated mild ($n = 83$), complicated mild ($n = 26$), or moderate, severe, or penetrating ($n = 46$) traumatic brain injury (TBI). We hypothesized that higher levels of tau and Aβ42 would be related to reduced neurocognitive performance and white matter integrity. Participants were enrolled prospectively from Walter Reed National Military Medical Center. Participants completed a blood draw, neuropsychological assessment, and diffusion tensor imaging (General Electric 3T) of the whole brain. From 20 neuropsychological test scores, five cognitive domain scores were computed. Measures of fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD) were generated for 18 regions of interest (ROIs). There was no relationship found between the plasma biomarkers and neurocognitive performance in any of the three TBI groups (all ps >0.05; all R^2 changes <0.146). Although not reaching statistical significance after correction for multiple comparisons, higher tau and Aβ42 tended to be related to higher FA and lower MD, RD, and AD in patients with a history of moderate, severe, or penetrating TBI. There was no consistent relationship between either of the biomarkers and white matter integrity in the complicated and uncomplicated mild TBI groups. In addition, there was no significant relationship between the biomarkers and age, education, sex, race, bodily injury severity, time since injury, TBI severity, or number of TBIs (all ps >0.15). Future investigation in larger samples of moderate, severe, and penetrating TBI are needed. Other plasma biomarkers, including phosphorylated tau, exosomal tau, and interleukin-10, may be more promising measures to use in the diagnosis, management, and treatment of TBI.

Keywords: amyloid; military; tau; traumatic brain injury; white matter integrity

Introduction

Traumatic brain injury (TBI) is one of the most common injuries of recent military operations with 383,947 service members with a diagnosis of at least one TBI between 1/1/2000 and 3/31/2018.[1] Outcome from TBI is variable. Most individuals who sustain a mild TBI recover completely within a few months of injury[2]; however, a large proportion of military service members with a history of TBI remain symptomatic for years.[3]

While it is not uncommon for patients with moderate, severe, or penetrating TBI to have good functional outcomes after their injury,[4–7] many of these patients experience lasting neurocognitive deficits.[8,9] Given the variability in recovery after TBI, there is much interest in identifying biomarkers that can reliably identify TBI and predict which patients will be likely to recover quickly and completely, and which patients are more likely to have prolonged and/or incomplete recovery.

Peripheral tau has been suggested as one such biomarker. Tau is a microtubule-associated protein that can become hyperphosphorylated

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and create intraneuronal neurofibrillary tangles. Investigation of plasma tau, which only requires a blood draw, has been of recent interest because it is relatively inexpensive and non-invasive. Plasma tau levels have been shown to be higher in Olympic boxers,[10] civilians with mild, moderate, or severe TBI,[11,12] and service members with a history of TBI[13] compared with controls.

Plasma tau levels seem to increase with increasing injury severity, because they are related to length of post-traumatic amnesia[11] and neuroimaging findings.[11,14] Plasma tau has also been shown to be higher in service members with three or more TBIs compared with service members with fewer than three TBIs.[13] Although plasma tau levels have been shown to increase immediately after a concussion,[15] boxing match,[10] or football practice,[16] they ultimately return to pre-injury levels in patients with concussion.[15] Plasma tau levels have been shown to remain elevated for at least 90 days after moderate-severe TBI.[11]

Increased levels of plasma tau have been shown to be related to increased cognitive decline in patients with Alzheimer disease and mild cognitive impairment,[17,18] suggesting that the neurological processes driving cognitive decline also result in elevated plasma tau. Despite the apparent increase in plasma tau after TBI, plasma tau does not appear to be related to cognition in repetitive subconcussive head impact.[19,20] It could be that this relationship is only apparent after more severe injury; however, to our knowledge, no studies have investigated the relationship between plasma tau and cognition in moderate-severe TBI.

Plasma tau has been shown to be related to some neuroimaging metrics in patients with TBI. Di Battista and colleagues[21] found a stronger correlation between peripheral tau level and cerebral blood flow and global neural connectivity in recently concussed athletes compared with non-concussed athletes and athletes with a history of remote concussion. The authors speculated this may be the result of a compromised glymphatic system resulting in diminished cerebral waste removal. In contrast, there does not appear to be a relationship between plasma tau and cerebral volumes in patients with concussion.[20]

To date, no studies have investigated the relationship between plasma tau and white matter integrity in humans with a history of TBI. Animal studies show that activated microglia, astrocytes, and elevated levels of proinflammatory molecules are found in the regions affected by glial and neuronal tau pathology.[22] In addition, cellular alterations such as cytotoxic edema, axonal injury, astrogliosis, activated microglia, and neuronal death after TBI can result in altered white matter integrity (see Hutchinson and coworkers[23] for a review).

For example, changes in axon morphology are expected to reduce anisotropy and diffusion along the axial direction; demyelination (loss of oligodendrocytes) is associated with decreased anisotropy and/or increased diffusion along the radial direction; while reactive astrogliosis/glial scarring is expected to reduce diffusivity and increase anisotropy, but activated microglia is associated with increased diffusivity.

Peripheral amyloid-beta 42 (Aβ42) is another blood biomarker thought to be affected by brain injury. It is a product of amyloid precursor proteins and forms extracellular plaques that interfere with neuronal functioning. An increase in plasma Aβ42 may be the result of a breakdown of the blood–brain barrier after TBI.[24] Patients with severe TBI have been shown to have higher levels of plasma Aβ42 than controls within the first week of injury.[24,25] Patients with complicated mild, moderate, or severe TBI were found to have higher levels of plasma Aβ42 than controls at 0, 30, and 90 days post-injury. In addition, plasma Aβ42 at 30 days post-injury was related to global outcome.[11] Within patients with severe TBI, plasma Aβ42 has been shown to increase with severity, with non-survivors having higher levels than survivors.[24]

No studies have examined how peripheral Aβ42 relates to neurocognitive performance or neuroimaging in patients with a history of TBI. In studies of older adults, however, cerebrospinal fluid and positron-emission tomography (PET) Aβ42 have been shown to be related to white matter integrity.[26–29] Similarly, a recent meta-analysis found that, regardless of method used to measure amyloid, Aβ42 was related to cognitive performance in older adults without cognitive impairment.[30]

Although plasma tau and Aβ42 appear to increase after TBI, whether plasma tau and Aβ42 levels relate to white matter integrity in patients with a history of TBI has yet to be investigated. Similarly, no studies have examined the relationship between plasma tau/Aβ42 and neurocognition in a TBI sample, although for tau, this relationship has been examined in two samples with repetitive subconcussive head injury (but not necessarily TBI).[19,20] The goal of the present study was to investigate the relationship between plasma tau and Aβ42, cognitive performance, and white matter integrity in patients with mild, moderate, severe, and penetrating TBI. We hypothesized that higher levels of tau and Aβ42 would be related to reduced neurocognitive performance and white matter integrity.

Methods

Participants

Participants were 197 U.S. military service members enrolled prospectively in a larger study designed to examine the natural history of recovery from TBI in service members and veterans (i.e., 15-Year Longitudinal TBI Study, Defense and Veterans Brain Injury Center [DVBIC]). Patients were targeted for recruitment and consent to the larger study if they presented to Walter Reed National Military Medical Center (WRNMMC; Bethesda, MD) after an uncomplicated mild, complicated mild, moderate, severe, or penetrating TBI or if they did not sustain a TBI.

Participants were recruited from three primary sources at WRNMMC: (a) hospital inpatient wards (2010–2018), (b) DVBIC outpatient TBI clinic (2010–2016), (c) National Intrepid Center of Excellence (NICoE) intensive outpatient TBI program and outpatient TBI clinic (2017–2018). Patients were identified for potential inclusion via daily reviews of consecutive hospital admissions and/or attendance at outpatient clinics.

Participants were enrolled in the larger study if they were an active-duty service member or other Defense Enrollment Eligibility Reporting System (DEERS)-eligible (i.e., eligible to receive military benefits) veteran; and 18 years of age or older who could read and understand English. General exclusion criteria included: a lack of proficiency in conversational English or a history of significant neurological or psychiatric condition(s) unrelated to the injury event or deployment (e.g., meningioma, bipolar disorder).

For the purposes of this study, participants were selected from a larger sample of 209 patients who had ($n = 164$) or had not ($n = 45$) sustained TBI and had completed a blood draw. Patients were selected for inclusion in the final sample if they had tau and Aβ42 levels with a coefficient of variation less than 0.20. This resulted in a final sample of 155 participants with a history of TBI and 42 controls. For many of the analyses, participants were separated into four groups: (1) controls (no lifetime history of TBI), (2) uncomplicated mild TBI, (3) complicated mild TBI, (4) moderate+ TBI (moderate, moderate-severe, severe, or penetrating TBI).

For the analyses investigating the relationship between tau/Aβ42 and cognition in TBI patients, patients were excluded if they failed performance validity tests or symptom validity tests (specific criteria described below), did not complete the Post-traumatic Stress Disorder Checklist—civilian version (PCL-C), or did not complete each of the 20 measures included in the cognitive domain scores, resulting in a final sample size of 114. For analyses investigating the relationship between tau/Aβ42 and white matter integrity in patients with TBI, patients were excluded if they did not undergo magnetic resonance imaging (MRI) scanning or if the scan was of insufficient quality to compute all targeted diffusion tensor imaging (DTI) metrics, resulting in a final sample size of 88.

TBI evaluation and classification

Diagnosis and classification of TBI were based on information gathered via medical record review and a comprehensive lifetime TBI history interview undertaken by clinical research personnel. The comprehensive lifetime TBI history interview was completed by Masters-level clinical research personnel who were trained specifically (by RTL and SML) to evaluate the presence and severity of TBI.

The TBI history interview consisted of the Ohio State University TBI identification method and an extended semi-structured clinical interview designed to (a) extract more detailed information to estimate the presence/duration of loss of consciousness (LOC), post-traumatic amnesia (PTA), alteration of consciousness (AOC), and retrograde amnesia, and (b) gather military-specific information regarding injury circumstances (e.g., type of blast, protection worn, etc.). Note that a simple self-report of being ''dazed and confused'' was not considered sufficient evidence to establish the presence of AOC.

During the interview, every effort was made to distinguish between ''confirmed'' AOC (i.e., confusion from brain injury as evidenced by reports of the person acting unusually, talking unusually, unable to follow simple commands, etc.) versus ''questionable'' AOC (i.e., confusion from simply being startled or surprised, or from pain or psychological factors).

Final determination and classification of TBI severity was undertaken by consensus, giving consideration to all information, during case conferencing with the interviewer and a PhD-level clinician/scientist trained in neuropsychology and TBI (RTL and SML). The TBI severity was classified as follows:

- (a) uncomplicated mild TBI ($n = 83$): (i) Glasgow Coma Scale (GCS) = 13–15, PTA <24 h, LOC <30 min, and/or AOC present, and (ii) no trauma-related intracranial abnormality (ICA) on computed tomography (CT) or structural MRI.
- (b) complicated mild TBI ($n = 26$): (i) GCS = 13–15, PTA <24 h, LOC <30 min, and/or AOC present, and (ii) trauma-related intracranial abnormality on CT or MRI (including epidural hemorrhage, subdural hematoma, subarachnoid hemorrhage, and susceptibility weighted imaging microhemorrhage that the radiologist attributed to TBI).
- (c) moderate TBI ($n = 10$): LOC 1–24 h, PTA 1–7 days, and ICA present or absent.
- (d) severe TBI ($n = 14$): LOC >24 h, PTA >7 days, and ICA present or absent.
- (e) penetrating TBI ($n = 17$): a breach of the cranial vault and/or dura mater by an external object (e.g., bullet, shrapnel) and/or skull fragment (i.e., skull fracture).

In addition, five patients were classified as having a ''moderate-severe TBI,'' given unclear information regarding duration of LOC and PTA and unreliable/unavailable GCS.

Measures and procedure

Participants completed a 5 h neuropsychological battery, a 1.5 h MRI brain scan, and a blood draw. All individuals completed these measures as part of a two-day evaluation that also included clinical interviews and a variety of neurobehavioral and neurocognitive measures.

Laboratory analyses. Non-fasting blood samples were collected with plastic lithium heparin tubes, processed within an hour of the sampling using standard protocols,[13] and stored at −80°C. Batch assays were conducted after all samples had been collected. Simoa™ (Quanterix, Lexington, MA), a high-definition-1 analyzer, was used to measure tau and Aβ42 concentrations. These methods have been published previously (Rissin and associates., 2011). All assays were randomized over plates and run in duplicate with laboratory scientists blinded to participant groups. Blood samples were not used if the reported coefficients of variation (CV) were over 20%. The average CVs were 4.7% for tau and 3.0% for Aβ42. The limit of detection for the assay is 0.012 pg/mL for tau and 0.044 pg/mL for Aβ42.

Bodily injury severity. Bodily injury severity was measured using the Injury Severity Score (ISS) derived from the Abbreviated Injury Scale.[31] On the ISS, higher scores are associated with increased injury severity. For the current study, a modified ISS that excluded intracranial injuries was calculated.

Neuropsychological assessment. Twenty neurocognitive measures were selected from the larger test battery. Four neurocognitive scores contributed to each of five cognitive domains:

- (1) Attention: Connor Continuous Performance Test-2 (CPT-II)[32] Omissions and Hit Reaction Time Standard Error T-Scores, and Wechsler Adult Intelligence Scale-4 (WAIS-4)[33] Digit Span and Letter-Number Sequencing Scaled Scores.
- (2) Processing Speed: WAIS-4 Coding and Symbol Search Scaled Scores, Delis-Kaplan Executive Function System (D-KEFS)[34] Word Reading Scaled Score, and Trail Making Test[35] Trial A T-Score.[36]
- (3) Immediate Memory: California Verbal Learning Test-II (CVLT-II)[37] Total Learning T-Score, Neuropsychological Assessment Battery (NAB)[38] Daily Living Memory Immediate Recall T-Score, and Wechsler Memory Scale-4 (WMS-4)[39] Logical Memory 1 and Visual Reproduction 1 Scaled Scores.
- (4) Delayed Memory: CVLT-II Long Delay Free Recall z score, NAB Daily Living Memory Delayed Recall T-Score, and WMS-4 Logical Memory 2 and Visual Reproduction 2 Scaled Scores.
- (5) Executive Functioning: D-KEFS Verbal Fluency Category Switching and Color Word Interference Test Inhibition Scaled Scores, NAB Categories Test T-Score, and WAIS-4 Similarities Scaled Score.

All scores were converted to scaled scores, and a cognitive domain summary score was calculated that represents the average of the four measures contributing to each domain. In addition to the five cognitive domain scores, an overall test battery mean (OTBM) was computed by averaging the five index scores.

Patients were also administered at least one stand-alone performance validity test (PVT; Medical Symptom Validity Test (MSVT),[40] Test of Memory Malingering (TOMM),[41] or Advanced Clinical Solutions Word Choice Test (WCT)[42] and multiple embedded measures of performance validity (WAIS-IV Reliable Digit Span, Logical Memory, and Visual Reproduction). Failure of either the stand-alone PVT and/or of at least two embedded measures

resulted in exclusion from the neuropsychological analyses. For the MSVT, failure was defined by cutoffs in the manual. For the WCT and all embedded measures, failure was defined as performance below the 10%ile.[42] For the TOMM, failure on Trial 2 was defined by the cutoff in the manual and failure on Trial 1 was defined using the cutoff recommended by Denning.[43]

Participants also completed the PCL-C,[44] and the Minnesota Multiphasic Personality Inventory-2nd Edition-Restructured Format (MMPI-2-RF).[45] When PCL-C data were used in the analyses, participants were not included in the study if they were considered to have exaggerated symptoms on the MMPI-2-RF (i.e., F-r ≥100T or Fp-r ≥90T or Fs ≥100T or FBS-r ≥100T or RBS ≥100T) or if their scores were not considered interpretable (i.e., Cannot Say scores >14, or VRIN-r/TRIN-r scores >79T).

MRI/DTI acquisition, processing and analysis. The MRI was performed on a 3T 750 MRI scanner (General Electric, Milwaukee, WI) with a 32-channel head coil. Diffusion-weighted imaging (DWI) was acquired by using a single shot echo planar imaging (EPI) sequence with slice-selection gradient reversal and peripheral cardiac-gating (repetition time/echo time [TR/TE] $\sim$10000/90 msec, field of view [FOV] = 256×256 mm^2, matrix = 128×128, voxel size $2 \times 2 \times 2$ mm^3, b = 1000 s/mm^2, 48 noncollinear diffusion gradient directions plus seven volumes of non-diffusion weighted [b0] evenly distributed among diffusion-weighted volumes).

Pre-processing of DTI data included correction of EPI geometric distortion using B0 fieldmap[46] correction of motion and eddy current artifacts and digital brain extraction (skull stripping) using software from the FSL toolkits (http://www.fmrib.ox.ac.uk/fsl).[47] A mean non-diffusion (b0) image was created by selecting the temporally central b0 image volume, and aligning the other six b0 images to it using rigid body transformation. The diffusion-weighted images were then aligned to the mean b0 image using the FLIRT affine transformation[48] with 12 degrees of freedom (DOF) to correct for subject head motion and the effects of eddy currents.

Diffusion gradient directions were modified and adjusted simultaneously according to the transformation. The brain was then extracted from the mean b0 image using BET[49] to define the brain, and then removing or masking out non-brain tissue in each of the DWI three-dimensional volumes. The DTI scalar image, fractional anisotropy (FA), was created using a simple least squares fit for single tensor reconstruction method.

An automated method reconstructing probabilistic distributions of major white matter tracts from each participant's native diffusion images based on the Bayesian framework for global probabilistic tractography[50] was used to segment major white matter tracts. This method, performed through the TRActs Constrained by UnderLying Anatomy (TRACULA),[51] uses a tract atlas of manually labeled tracts and FreeSurfer anatomical segmentations from a set of training subjects to obtain the probability of each tract traversing or neighboring the anatomical segmentations along its trajectory.

For manual labeling of white matter pathways from a training data set, the locations of regions of interest (ROIs) that the pathways traverse were identified based on the well-established protocols.[52] The knowledge on white matter pathways, which were labeled manually from a training set consisting of healthy subjects, was extracted and then used to initialize global tractography by constraining its search space and pathway based on the prior anatomical knowledge. In other words, these anatomical priors are incorporated in a probabilistic framework to guide tractography in each novel subject. Specifically, at least two anatomical locations that the pathway is known to traverse were drawn with additional ROIs to eliminate streamlines that were not belonging to the pathway of interest.

For automated segmentation of white matter tracts, a Bayesian framework for global tractography based on ball-and-stick model[50] parameters was applied to estimate the posterior distribution of each pathway connecting two regions—i.e., start seed ROI and end ROI. Therefore, this method allows for individual variation while reconstructing tracts that are anatomically consistent across individuals and has been shown to reconstruct tracts accurately in individual subjects (compared with manual labeling) using anatomical priors.

Segmented and labeled fiber tracts included 18 ROIs that consisted of (a) corpus callosum-forceps major, (b) corpus callosum-forceps minor, and (c) two unilateral symmetrical ROIs (left/right) each for the anterior thalamic radiation, cingulum-angular (infracallosal) bundle, cingulum-cingulate gyrus (supracallosal) bundle, corticospinal tract, inferior longitudinal fasciculus, superior longitudinal fasciculus-parietal bundle, superior longitudinal fasciculus-temporal bundle, and uncinate fasciculus.

Measures of FA, mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD) were generated for the 18 ROIs. In addition, a ''whole brain'' measure was calculated by averaging the mean scores across all 18 ROIs for each of the four DTI metrics. All ROIs were included because no studies have examined the relationship between plasma tau/Aβ42 and white matter integrity, and we therefore did not have any *a priori* hypotheses regarding which specific ROIs would be related to the plasma biomarkers.

Data analyses. Analysis of variance (ANOVA) and the Fisher Least Squared Difference (LSD) test were used to examine the differences between controls and the three TBI groups across demographics, injury characteristics, PCL-C total score, and the plasma biomarkers. Chi square tests were used to examine differences in sex and race between the four groups. The relationship between potential confounds and the biomarkers was evaluated via Pearson correlations and ANOVAs. Given the large number of DTI measures (i.e., FA, MD, RD, and AD across the 18 ROIs and whole brain), and that Type 1 error increases when multiple statistical comparisons are made, the Benjamini-Hochberg procedure[53] was used to keep the false discovery rate at 0.05. All other analyses were interpreted using a criterion of $p < 0.01$.

To examine the relationship between the biomarkers and neuropsychological performance, a series of hierarchical regressions were completed in the 114 participants with a history of TBI and valid, complete neuropsychological data. Because of the known influence TBI severity can have on neurocognitive performance,[54] these analyses were conducted in the uncomplicated mild TBI group ($n = 58$), complicated mild TBI group ($n = 23$), and moderate+ TBI group ($n = 33$) separately. The dependent variables included the five cognitive domains and the overall test battery mean.

The first step in the models included any covariates that were independently correlated with the dependent variable (all models included PCL-C total score; the models for attention also included age; the models for immediate memory also included race and bodily injury severity). The second step in the models included either plasma tau level or plasma Aβ42 level.

To examine the relationship between plasma tau and Aβ42 and white matter integrity, a series of hierarchical regression analyses were undertaken in the 88 participants with a history of TBI with neuroimaging data. Because TBI severity influences DTI results,[55] these analyses were run separately in the uncomplicated mild TBI group ($n = 47$), complicated mild TBI group ($n = 19$), and moderate+ TBI group ($n = 22$). Plasma tau and Aβ42 levels were the independent variables, and DTI measures (i.e., FA, MD, RD, and AD across the 18 ROIs and whole brain) were the dependent variables. Given the known influence of age on DTI measures,[56] age was included in the first step in each regression model as a covariate. Tau and amyloid were each entered separately in the second step of the model.

Results

Descriptive statistics and group comparisons for demographic and clinical characteristics by group (control, uncomplicated mild TBI, complicated mild TBI, moderate+ TBI) are presented in Table 1. There were no significant main effects across the four groups for age, education, sex, or PCL-C total score. The control group was evaluated closer to their date of injury than the uncomplicated mild TBI group (Fisher LSD $p = 0.004$, Cohen d = 0.66) and the moderate+ TBI group (Fisher LSD $p = 0.009$, Cohen d = 0.71). There were no other significant pairwise differences for time since injury between the groups.

The uncomplicated mild TBI group had a higher number of lifetime TBIs than the complicated mild TBI group (Fisher LSD $p = 0.019$, Cohen d = 0.48) and the moderate+ TBI group (Fisher LSD $p = 0.042$, Cohen d = 0.32). The control group and uncomplicated mild TBI group both had less severe bodily injuries than the moderate+ TBI group (Fisher LSD ps <0.03, Cohen ds = 0.58–0.65); the uncomplicated mild TBI group also had less severe bodily injuries than the complicated mild TBI group (Fisher LSD p = 0.041; Cohen d = 0.41). The uncomplicated mild TBI group was less likely to be white than the moderate+ TBI group ($\chi^2 = 5.133$, p = 0.023).

Descriptive statistics and group comparisons for plasma tau and Aβ42 levels are also presented in Table 1. There were no significant differences in plasma tau or Aβ42 levels between any of the groups (Fisher LSD ps >0.05). Cohen d effect sizes ranged from 0.08–0.41 (very small to small-medium) for tau and from 0.03–0.26 (very small to small) for Aβ42.

Biomarkers and demographics/clinical characteristics

The results of a series of correlation analyses between plasma tau and Aβ42 and age, education, time since injury, number of TBIs, bodily injury severity, and PCL-C total score are presented in Table 2. There were no significant relationships between the biomarkers and any of the aforementioned potential confounds (all ps >0.2). In addition, ANOVAs revealed no significant differences in tau or Aβ42 levels between males and females, or whites and non-whites (all ps >0.4).

Biomarkers and neuropsychological performance

There were no significant relationships between the plasma biomarkers and cognitive domain scores in any of the three TBI subsamples (all ps >0.05; all R^2 changes <0.146). R-squared change values associated with the second step of the models are presented in Table 3.

Biomarkers and white matter integrity

A summary of the beta values obtained after adding tau or Aβ42 into the models are presented in Tables 4 and 5, respectively. Although there were some consistent trends in the data, none of the individual analyses survived the Benjamini-Hochberg correction.

As shown in Table 4, in the uncomplicated mild TBI group, as tau increased, AD tended to increase in most ROIs. This relationship was strongest in the left cingulum-cingulate gyrus (supracallosal) bundle (R^2 change = 0.135, $p = 0.010$) and left superior longitudinal fasciculus-temporal bundle (R^2 change = 0.088, $p = 0.044$). In contrast, as tau increased, AD decreased in the forceps major (R^2 change = 0.161, $p = 0.006$) and right inferior longitudinal fasciculus (R^2 change = 0.089, $p = 0.041$) in uncomplicated mild TBI patients.

In the moderate+ TBI group, as tau increased, FA tended to increase in most ROIs. This relationship was strongest in the left (R^2 change = 0.271, $p = 0.015$) and right (R^2 change = 0.351, p = 0.003) inferior longitudinal fasciculi and left uncinate

Table 1. Descriptive Statistics and Group Comparisons for Demographics and Clinical Characteristics

	1. Controls (n = 42)		*2. Uncomplicated mild TBI (n = 83)*		*3. Complicated mild TBI (n = 26)*		*4. Moderate+ TBI (n = 46)*		*ANOVA*		*Fisher LSD pairwise comparisons $p < .05$*
Measures	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*F*	p	
Age (in years)	36.21	11.69	34.42	9.78	35.62	11.51	34.02	8.75	0.446	0.720	–
Education (in years)	14.21	1.97	14.59	2.11	14.58	2.59	14.61	2.30	0.330	0.804	–
Months since injury	33.50	36.44	61.35	60.08	49.38	45.92	62.15	47.33	3.286	0.022	1 < 2&4
Number of TBIs	n/a	n/a	1.45	0.70	1.15	0.37	1.24	0.57	67.615	<.001	3&4 < 2
Bodily injury severity[a]	6.76	8.12	6.19	8.07	10.15	12.37	10.96	7.00	3.897	0.010	1 < 4; 2 < 3&4
PCL-C total score[b]	31.21	12.43	33.03	15.29	36.00	16.16	29.74	12.17	1.046	0.374	–
Tau	2.81	1.20	2.90	1.06	3.29	1.13	3.20	1.12	1.705	0.167	–
Amyloid beta-42	8.12	1.83	8.18	2.09	8.41	2.12	8.63	2.14	0.629	0.597	–
	n	%	n	%	n	%	n	%	X^2	p	*Group comparisons $p < 0.05$*
Sex									1.542	0.673	–
Male	38	90.5	76	91.6	25	96.2	44	95.7			
Female	4	9.5	7	8.4	1	3.8	2	4.3			
Race									6.293	0.098	2 vs. 4
White	29	69	55	66.3	21	80.8	39	84.8			
Other	13	31	28	33.7	5	19.2	7	15.2			

LSD, least significant difference; ANOVA, analysis of variance; TBI, traumatic brain injury; M, mean; SD, standard deviation.

[a]Two people in the uncomplicated mild group were missing this data.

[b]Removed participants who failed symptom validity tests, so sample size reduced (controls $n = 33$; uncomplicated mild $n = 66$; complicated mild $n = 23$; moderate+ $n = 37$).

Table 2. Correlations between Plasma Tau and Aβ42 and Participant Characteristics ($N = 155$)

	Tau		*Amyloid-Beta 42*	
	r	p	*r*	p
Age	0.047	0.561	–0.099	0.223
Education	0.115	0.155	–0.004	0.957
Time since injury	0.090	0.267	0.021	0.795
Bodily injury severity[a]	–0.027	0.743	–0.025	0.759
Number of TBIs	–0.020	0.801	0.002	0.976
	F	p	*F*	p
Sex	0.279	0.598	0.520	0.472
Race	0.615	0.434	0.111	0.740

TBI, traumatic brain injury.
[a]n = 153 because 2 participants were missing data.

fasciculus (R^2 change = 0.205, $p = 0.028$). In contrast, MD and RD tended to be inversely related to tau in most ROIs, with this relationship most pronounced in the left corticospinal tract (R^2 change = 0.240-.246, ps = 0.016–0.018) and left superior longitudinal fasciculus-parietal bundle (R^2 change = 0.194–0.197, ps = 0.038–0.040). There was no relationship between tau and DTI metrics in the complicated mild group (all R^2 change = 0.179, ps >0.05).

As shown in Table 5, in the moderate+ TBI group, as Aβ42 increased, MD and RD tended to decrease in the whole brain (R^2 change = 0.204–0.242, ps = 0.020–0.033) and in most ROIs. This relationship was strongest in the forceps major (R^2 change = 0.299–0.303, ps = 0.009–0.010), right inferior longitudinal fasciculus (R^2 change = 0.234–0.349, ps = 0.005–0.024), right superior longitudinal fasciculus-parietal bundle (R^2 change = 0.194–0.196, ps = 0.027–0.035), and right superior longitudinal fasciculus-temporal bundle (R^2 change = 0.266–0.269, ps = 0.010–0.013). As Aβ42 increased, AD also tended to decrease in the whole brain (R^2 change = 0.241, $p = 0.023$) and across all ROIs, with this relationship most pronounced in the right inferior longitudinal fasciculus (R^2 change = 0.431, $p = 0.001$).

The FA tended to increase with Aβ42 across all ROIs, with this relationship most pronounced in the forceps major (R^2 change = 0.202, $p = 0.031$). There was no relationship between Aβ42 and DTI metrics in the uncomplicated mild (all R^2 change < 0.068, ps >0.05) or complicated mild TBI groups (all R^2 change < 0.119, ps >0.05).

Table 3. R^2 Change Values from Hierarchical Regressions Examining the Impact of Plasma Tau and Amyloid on Neuropsychological Test Results

	Uncomplicated mild (n = 58)		*Complicated mild (n = 23)*		*Moderate+ (n = 33)*	
Cognitive Index	*Tau*	*Aβ42*	*Tau*	*Aβ42*	*Tau*	*Aβ42*
OTBM	.010	.008	.009	.003	.001	.000
Attn	.008	.000	.002	.145	.013	.010
PS	.037	.014	.001	.041	.010	.028
Imm Mem	.002	.024	.000	.095	.002	.007
Del Mem	.007	.003	.006	.003	.000	.000
Ex Fx	.000	.008	.040	.000	.002	.001

OTBM, overall test battery mean; Attn, attention; PS, processing speed; Imm Mem, immediate memory; Del Mem, delayed memory; Ex Fx, executive functioning.

Discussion

This is the first study to examine the relationship between plasma tau and Aβ42, neurocognitive performance, and white matter integrity in patients with a history of TBI. There was no relationship found between the plasma biomarkers and neurocognitive performance in any of the TBI severity groups. Although not reaching statistical significance after correction for multiple comparisons, higher tau and Aβ42 tended to be related to higher FA and lower MD, RD, and AD in patients with a history of moderate, severe, or penetrating TBI. There was no consistent relationship, however, between either of the biomarkers and white matter integrity in the complicated and uncomplicated mild TBI groups. In addition, there was no significant relationship between the biomarkers and age, education, sex, race, bodily injury severity, time since injury, TBI severity, number of TBIs, or PTSD symptom report.

The finding that plasma tau and Aβ42 levels were unrelated to neurocognitive performance mirrors the null findings between plasma tau and cognition in patients with repetitive subconcussive head impact in the chronic stages of recovery.[19,20] It seems possible that plasma tau and Aβ42 may not be sufficiently sensitive to TBI many years after concussion or repetitive subconcussive head impact. Exosomal tau, however, which has been shown to be sensitive to concussion many years post-injury,[57,58] has been shown to be related to processing speed and verbal learning and memory[58] and may be a better biomarker of TBI and recovery than plasma tau.[57]

Although the relationship between plasma biomarkers and white matter integrity was not statistically significant after correction for multiple comparisons, there were consistent trends explaining roughly 20–30% of the variance between the biomarkers and ROIs that are worth highlighting. In patients with moderate, severe, or penetrating TBI, higher tau and Aβ42 tended to be related to higher FA and lower MD, RD, and AD.

The finding that MD, RD, and AD were inversely related, but FA was positively related to plasma tau/Aβ42 levels may be explained by the effects of axonal damage, astrogliosis, and glial scarring with increased cellularity and organization. These processes would result in decreased axial and radial diffusivity, and increased anisotropy.[23] Generally, changes in axon morphology are expected to reduce anisotropy and diffusion along the axial direction. Demyelination (loss of oligodendrocytes) is associated with decreased anisotropy and/or increased diffusion along the radial direction. Reactive astrogliosis/glial scarring is expected to reduce diffusivity and increase anisotropy, while activated microglia is associated with increased diffusivity.

There were some instances where plasma tau (i.e., in the left corticospinal tract, left superior longitudinal fasciculus-parietal bundle, and right anterior thalamic radiations) or Aβ42 (i.e., forceps major, right superior longitudinal fasciculus-parietal and temporal bundles) were inversely related to RD but not related to AD in the moderate+ TBI group. This might suggest reactive astrogliosis caused by chronic inflammation without axonal damage in these white matter tracts.[23] Unfortunately, reactive astrogliosis is not best evaluated by using single-tensor DTI.

The single-tensor DTI model used in this study is not able to differentiate intracellular diffusivity and extracellular diffusivity. Bi-tensor models such as free water imaging models would allow the separation of extracellular free water from water in the cellular tissue. This would allow for the evaluation of abnormalities in the

Table 4. Summary of Beta Coefficients Between Plasma Tau and All Diffusion Tensor Imaging Regions of Interest and the Whole Brain

	Uncomplicated mild (n = *47*)				*Complicated mild* (n = *19*)				*Moderate+* (n = *22*)			
	FA	*MD*	*RD*	*AD*	*FA*	*MD*	*RD*	*AD*	*FA*	*MD*	*RD*	*AD*
WHOLE BRAIN	.176	.002	−.076	.154	.125	.094	.019	.173	.383	−.350	−.385	−.181
F MAJOR	−.014	−.390[b]	−.223	−.408[b]	−.288	.010	.113	−.199	.149	−.353	−.262	−.329
F MINOR	.249	−.032	−.157	.171	−.080	.106	.119	.039	.395	−.316	−.369	−.104
L ATR	.172	−.007	−.092	.124	−.119	.021	.092	−.103	.269	−.288	−.331	−.060
L CAB	.120	.201	.118	.257	.178	.137	.081	.185	.196	−.018	−.056	.073
L CCG	.293	.165	−.133	.374[a]	.211	.126	−.061	.314	.438	−.264	−.419	.128
L CST	.047	.149	.058	.178	.066	.001	−.062	.059	.260	−.506[a]	−.511[a]	−.254
L ILF	−.195	−.015	.095	−.209	.102	.222	.155	.231	.537[a]	−.087	−.275	.354
L SLFP	.205	.148	−.026	.262	.140	−.041	−.107	.078	.250	−.455[a]	−.458[a]	−.350
L SLFT	.166	.252	.062	.301[a]	.244	.099	−.127	.257	.310	−.419	−.433	−.245
L UNC	.166	−.041	−.111	.105	−.182	.427	.440	.311	.467[a]	−.174	−.294	.120
R ATR	.159	.178	.067	.262	.089	.096	.044	.151	.392	−.327	−.438[a]	−.044
R CAB	.179	−.123	−.165	−.012	.161	.109	.023	.243	.029	.062	.032	.101
R CCG	.129	.095	−.055	.180	.120	−.109	−.139	−.036	.312	−.420	−.394	−.166
R CST	.060	.047	−.007	.089	−.106	.201	.179	.070	.129	−.315	−.288	−.231
R ILF	−.141	−.216	−.074	−.304[a]	.181	.047	−.037	.128	.611[b]	−.245	−.413	.145
R SLFP	−.003	.002	.016	−.020	.060	.142	.049	.170	.057	−.247	−.234	−.212
R SLFT	.137	−.013	−.081	.109	.068	.143	.044	.183	−.061	−.278	−.183	−.378
R UNC	−.041	.313[a]	.227	.281	.007	.053	.024	.075	.305	−.235	−.271	−.060

FA, fractional anisotropy; MD, median diffusivity; RD, radial diffusivity; AD, axial diffusivity; CCF major, corpus callosum-forceps major; CCF Minor, corpus callosum-forceps minor; ATR, anterior thalamic radiation; CAB, cingulum–angular (infracallosal) bundle; CCF, cingulum–cingulate gyrus (supracallosal) bundle; CST, corticospinal tract; ILF, inferior longitudinal fasciculus; SLFP, superior longitudinal fasciculus-parietal bundle; SLFT, superior longitudinal fasciculus-temporal bundle; UNF, uncinate fasciculus.

[a] $p < 0.05$.

[b] $p < 0.01$.

Table 5. Summary of Beta Coefficients between Plasma Aβ42 and All Diffusion Tensor Imaging Regions of Interest and the Whole Brain

	Uncomplicated mild (n = *47*)				*Complicated mild* (n = *19*)				*Moderate+* (n = *22*)			
	FA	*MD*	*RD*	*AD*	*FA*	*MD*	*RD*	*AD*	*FA*	*MD*	*RD*	*AD*
WHOLE BRAIN	.048	.059	.014	.117	.172	−.119	−.169	−.009	.390	−.547[a]	−.502[a]	−.546[a]
F MAJOR	.054	−.061	−.077	−.003	.277	−.215	−.254	−.097	.499[a]	−.612[a]	−.608[b]	−.218
F MINOR	.013	.150	.106	.131	.343	−.245	−.316	.005	.173	−.394	−.336	−.424
L ATR	−.135	.191	.200	.060	.198	.009	−.083	.150	.077	−.385	−.295	−.363
L CAB	.180	.001	−.081	.127	.035	−.126	−.132	−.101	.414	−.362	−.393	−.235
L CCG	−.133	.051	.153	−.119	.186	−.160	−.217	.074	.025	−.286	−.199	−.229
L CST	−.039	−.018	.008	−.043	−.005	−.062	−.019	−.043	.189	.026	−.048	.109
L ILF	.120	−.103	−.146	.024	.047	−.101	−.078	−.097	.225	−.432	−.370	−.455
L SLFP	.048	.041	−.002	.066	−.122	−.170	−.075	−.229	.193	−.253	−.238	−.223
L SLFT	.078	.246	.090	.260	−.186	−.067	.085	−.172	.194	−.149	−.170	−.056
L UNC	.144	−.083	−.126	.027	.058	−.010	−.014	−.004	.165	−.170	−.165	−.1 42
R ATR	−.037	.192	.164	.146	−.104	−.175	−.092	−.253	.130	−.429	−.390	−.330
R CAB	.049	.032	.021	.044	.246	−.042	−.111	.097	.174	−.455[a]	−.409	−.428
R CCG	−.154	.127	.189	−.050	.236	.107	−.052	.217	.068	−.383	−.253	−.420
R CST	−.013	.033	.019	.030	.268	−.129	−.257	.084	.161	−.416	−.308	−.431
R ILF	.067	−.081	−.101	−.016	.040	.002	.013	−.009	.273	−.657[b]	−.537[a]	−.729[b]
R SLFP	.025	−.036	−.018	−.043	.065	−.106	−.113	−.042	.249	−.492[a]	−.489[a]	−.392
R SLFT	−.026	−.023	.022	−.087	.079	.020	−.015	.048	.448	−.573[a]	−.576[a]	−.412
R UNC	.016	.046	.027	.051	.019	.177	.114	.192	.348	−.300	−.314	−.181

FA, fractional anisotropy; MD, median diffusivity; RD, radial diffusivity; AD, axial diffusivity; CCF major, corpus callosum-forceps major; CCF Minor, corpus callosum-forceps minor; ATR, anterior thalamic radiation; CAB, cingulum–angular (infracallosal) bundle; CCF, cingulum–cingulate gyrus (supracallosal) bundle; CST, corticospinal tract; ILF, inferior longitudinal fasciculus; SLFP, superior longitudinal fasciculus-parietal bundle; SLFT, superior longitudinal fasciculus-temporal bundle; UNF, uncinate fasciculus.

[a] $p < 0.05$

[b] $p < 0.01$

extracellular space such as neuroinflammation, and for tissue abnormalities such as axonal degeneration. Other advanced diffusion MRI techniques such as diffusion kurtosis imaging[59] and multi-compartment modeling using multi-shell diffusion MRI would be more useful to evaluate the underlying mechanisms multiple years after a TBI.

The trend of higher tau being related to higher FA consistently in the moderate+ TBI group is initially somewhat counterintuitive, because generally one would expect FA to decrease with increasing brain damage. The FA, however, is generally proportional to the ratio of AD to RD, with FA values increasing as the ratio of AD to RD becomes more prominent. Indeed, in ROIs where FA and tau were significantly directly correlated, the AD and tau tended to be positively correlated rather than negatively correlated. This suggests that two major mechanisms may play a role: (1) the presence of astrogliosis (an increase in AD)[23,60] and (2) the presence of plaques or other diffusion hindering material.[60,61]

Although the majority of studies find decreased FA in moderate-severe TBI samples,[62] some studies have found increased FA in some regions in TBI samples.[63–65] This increase in FA has been attributed to the coherent organization of reactive astrogliosis over the perilesional cortex in the subacute TBI rat model[66] or axonal regrowth in patients with severe TBI in the chronic stage of recovery.[64]

The relationship between the plasma biomarkers and DTI metrics was more variable in the uncomplicated mild TBI group. Higher tau was related to lower AD in some ROIs (forceps major, right inferior longitudinal fasciculus) and higher AD in other ROIs (left cingulum-cingulate gyrus (supracallosal) bundle). In addition, higher tau was related to lower MD in the forceps major, but higher MD in the right uncinate fasciculus. There were no significant relationships between Aβ42 and white matter integrity in the uncomplicated mild TBI group.

Overall, it seems most likely that these findings in the uncomplicated mild TBI group are the spurious result of conducting a large number of comparisons. Further supporting the idea that these were false-positive findings are that these relationships were not replicated in the complicated mild TBI group or the moderate TBI group. In fact, there were no significant relationships between the plasma biomarkers and any DTI metrics in the complicated mild TBI group. Although the sample size of the complicated mild group was limited ($n = 19$), it was only slightly smaller than the moderate+ TBI group ($n = 22$), where multiple correlations were considered significant before application of the Benjamini-Hochberg correction.

Intuitively, it makes sense that findings would be limited to the moderate+ group because there should be more variability in DTI metrics in this group. Although there were signs of a possible relationship between plasma biomarkers and white matter integrity in the moderate+ TBI group, none of these relationships survived a correction for multiple comparisons.

The small sample size is a major limitation of this study. Further research in larger samples is needed to confirm these findings. An additional limitation is that our moderate+ group was limited to patients who were able to travel to and participate in a multi-day study. Many patients with severe TBI are unable to consent to participate in treatment, negotiate long distance travel, and/or undergo such extensive assessments. It is possible that including patients with more severe injuries who were unable to participate in this study would result in stronger relationships between the biomarkers and outcome measures.

Another limitation is the relatively long time since injury of our sample. It is possible that the lack of a relationship between the plasma biomarkers and TBI characteristics was driven by the relatively long time since injury. A previous study investigating plasma tau in service members in the chronic phase of recovery from TBI found that time since injury was unrelated to peripheral tau levels;[13] however, plasma tau may increase immediately after TBI and return to normal levels within six months of injury.[10,12,15] Although unrelated to most TBI severity and outcome variables in the present study, it is possible that plasma tau and Aβ42 may be related to these variables in the acute or subacute phase of recovery.

A final limitation is that the derivations of the plasma biomarkers are unknown. It is unclear whether their levels are the result of neuronal damage from the TBI, secondary peripheral causes, or factors unrelated to the TBI.

It is possible that the lack of relationship between plasma tau and Aβ42 and all other variables of interest reflects that plasma tau and Aβ42 are not the pre-eminent biomarkers of brain damage at any time point. Indeed, there were no differences in plasma tau and Aβ42 between controls and any of the TBI groups. Other plasma biomarkers, including phosphorylated tau, exosomal tau, and interleukin-10, have been shown to be increased in TBI samples[12,58,67] and to be related to severity of injury[12,57] and number of TBIs.[57] These may be more promising measures to use in the diagnosis, management, and treatment of TBI.

The pursuit of a reliable plasma biomarker to diagnose and aid in management of TBI is worthwhile. The reliance on self-report and frequently non-existent or sparse medical records to diagnose TBI is a major limitation on both TBI research and treatment. Incorrect classification of TBI participants versus controls certainly confounds research results. Incorrectly treating a patient for a TBI they have not incurred likely has major iatrogenic consequences,[68–70] while failing to manage an unidentified TBI also has clear negative clinical implications.[71] Biomarkers that could reliably identify TBI and inform treatment and prognosis would be extremely beneficial for research and clinical work.

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Author Disclosure Statement

The views expressed in this manuscript are those of the authors and do not reflect the official policy of the Department of Army, Navy, Air Force, Department of Defense, or U.S. Government. The identification of specific products, scientific instrumentation, or organizations is considered an integral part of the scientific endeavor and does not constitute endorsement or implied endorsement on the part of the author, DoD, or any component agency.

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