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Longitudinal Associations among Posttraumatic Stress Disorder Symptoms, Traumatic Brain Injury, and Neurocognitive Functioning in Army Soldiers Deployed to the Iraq War

Jennifer J. Vasterling,[1,2] Mihaela Aslan,[3,4] Lewina O. Lee,[2,5] Susan P. Proctor,[5,6,7] John Ko,[3] Shawna Jacob,[8] AND John Concato[3,4]

[1]National Center for PTSD and Psychology Service, VA Boston Healthcare System, Boston, Massachusetts
[2]Department of Psychiatry, Boston University School of Medicine, Boston, Massachusetts
[3]Clinical Epidemiology Research Center, VA Cooperative Studies Program, West Haven, Connecticut
[4]Department of Medicine, Yale University School of Medicine, New Haven, Connecticut
[5]Research Service, VA Boston Healthcare System, Boston, Massachusetts
[6]US Army Research Institute of Environmental Medicine, Natick, Massachusetts
[7]Department of Environmental Health, Boston University School of Public Health, Boston, Massachusetts
[8]Psychology Service, VA Boston Healthcare System, Boston, Massachusetts

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Abstract

Objectives: Military deployment is associated with increased risk of adverse emotional and cognitive outcomes. Longitudinal associations involving posttraumatic stress disorder (PTSD), relatively mild traumatic brain injury (TBI), and neurocognitive compromise are poorly understood, especially with regard to long-term outcomes, and rigorous research is necessary to better understand the corresponding relationships. The objective of this study was to examine short-term and long-term (>5 years) longitudinal associations among PTSD, neurocognitive performance, and TBI following military deployment. **Methods:** In this prospective study, $N = 315$ U.S. Army soldiers were assessed at military installations before (2003–2005) and after (2004–2006) an index deployment to the Iraq War, and again an average of 7.6 years later (2010–2014) as a nationally dispersed cohort of active duty soldiers, reservists, and veterans. Thus, the study design allowed for two measurement intervals over which to examine changes. All assessments included the PTSD Checklist, civilian version, and individually-administered performance-based neurocognitive tests. TBI history was derived from clinical interview. **Results:** Autoregressive analyses indicated that visual reproduction scores were inversely related to subsequent PTSD symptom severity at subsequent assessments. Conversely, increases in PTSD symptom severity over each measurement interval were associated with poorer verbal and/or visual recall at the end of each interval, and less efficient reaction time at post-deployment. TBI, primarily mild in this sample, was associated with adverse PTSD symptom outcomes at both post-deployment and long-term follow-up. **Conclusions:** These results suggest longitudinal relationships among PTSD symptoms, TBI, and neurocognitive decrements may contribute to sustained emotional and neurocognitive symptoms over time. (*JINS*, 2018, *24*, 311–323)

Keywords: Cognitive function, Posttraumatic stress disorders, Military personnel, Veterans, Traumatic brain injury, War exposure

INTRODUCTION

Contemporary warfare increases the risk of various adverse and functionally relevant psychiatric and neuropsychiatric outcomes, including posttraumatic stress disorder (PTSD) (Eekhout, Reijnen, Vermetten, & Geuze, 2016; Vasterling et al., 2016) and neurocognitive alterations (Vasterling, Proctor, Amoroso, Kane, Heeren, et al., 2006). The relationship of combat stress to PTSD is well documented (Ramchand, Rudavsky, Grant, Tanielian, & Jaycox, 2015), but the etiology of neurocognitive compromise in war veterans is less clear. Mild traumatic brain injury (mTBI), a prevalent injury of the wars in Iraq and Afghanistan, has been purported to be a potential source of neurocognitive impairment among warzone veterans. Although there is substantial evidence of acute effects of mTBI on neurocognition (Rabinowitz & Levin, 2015), meta-analytic studies suggest that recovery

Correspondence and reprint requests to: Jennifer J. Vasterling, Psychology (116B), VA Boston Healthcare System, 150 S. Huntington Avenue, Boston, MA 02130. E-mail: jennifer.vasterling@va.gov

typically occurs within 90 days for most milder TBI events (e.g., Karr, Areshenkoff, & Garcia-Berrera, 2014). The longer-term impact of deployment-related mild TBI on neurocognitive functioning, however, has been debated, with some evidence suggesting that PTSD and other common psychiatric co-morbidities of deployment TBI may substantially contribute to neurocognitive compromise in warzone veterans with history of mild TBI (e.g., Neipert et al., 2014; Vasterling et al., 2012; Verfaellie, Lafleche, Spiro, & Bousquet, 2014).

Service members and military veterans may also engage in health risk behaviors (e.g., increased alcohol use, reckless driving) associated with PTSD (Kelley et al., 2012) that place them at risk for non-deployment TBI subsequent to their return from warzone participation (Regasa, Thomas, Gill, Marion, & Ivins, 2016), but the effects of non-deployment injuries on long-term psychiatric and neurocognitive outcomes among contemporary war zone veterans has received little attention.

The interplay among PTSD, TBI, and neurocognitive functioning is likely complex. As summarized in a recent review (Arnsten, Raskind, Taylor, & Connor, 2015), the animal literature has suggested that the neurocognitive impairment observed in cross-sectional studies of PTSD in humans (Scott et al., 2015) may be attributable to chronic neurobiological disturbances arising from exposure to extreme stress and maintained by PTSD. Evidence from prospective studies of trauma-exposed human populations, however, suggests that pre-exposure neurocognitive performance can moderate the effects of trauma exposure on PTSD development (Marx, Doron-Lamarca, Proctor, & Vasterling, 2009; Parslow & Jorm, 2007).

Although the mechanisms are not as yet fully understood, greater neurocognitive integrity has been purported to buffer the effects of traumatic stress by enhanced cognitive control of trauma memories, stronger regulation of emotions, and the adaptive re-appraisal of trauma-related cognitions requiring both the inhibition of maladaptive thoughts and the generation of more constructive alternatives. Such bi-directional influences, if present, would potentially create a downward spiral, in which both neurocognitive impairment and PTSD symptoms increase over time. In addition, recent prospective studies of relatively short-term outcomes have indicated that deployment TBI increases risk of PTSD from 3 to 12 months after return from deployment (Mac Donald et al., 2017; Stein et al., 2015).

Better understanding of longitudinal associations among common risk factors and emotional and neurocognitive outcomes of warzone deployment may inform points of intervention. Much of the existing research, however, has been cross-sectional, limiting the ability to make causal inferences. As part of Veterans Affairs (VA) Cooperative Studies Program #566 (CSP#566), we examined data gathered prospectively from U.S. Army soldiers before (2003–2005) and after (2004–2006) Iraq War deployment, and again at a long-term (>5-year) follow-up assessment (2010–2014). Our goal was to examine the longitudinal associations among PTSD, neurocognitive performance, and TBI following military deployment. Taking into account prior values of outcome variables and adjusting for age, education, race/ethnicity, marital status, military duty status, and combat severity, we hypothesized that for both post-deployment and long-term follow-up outcomes: (1) increases in PTSD symptom severity would be associated with less favorable neurocognitive outcomes; (2) more proficient neurocognitive performance at prior assessments would be associated with less severe PTSD symptoms at subsequent assessments; and (3) TBI (predominantly mild and uniformly post-acute in this sample) would be associated with more severe PTSD symptoms, but would not be associated with neurocognitive outcomes.

METHODS

Sampling and Recruitment

Human subjects approval was obtained from the VA Central Institutional Review Board. All participants provided written, in-person consent for neurocognitive data used in the current analyses; other data (e.g., details of TBI episodes) used in models were obtained previously *via* verbal, telephone consent.

The current study is a component of a longitudinal cohort study (Neurocognition Deployment Health Study) (Vasterling, Proctor, Amoroso, Kane, Gackstetter, et al., 2006) that has included pre-deployment, post-deployment, and long-term follow-up (CSP#566) assessments that were conducted in reference to an index Iraq War deployment for each participant. NDHS participants were sampled as U.S. Army soldiers at the military battalion level before their deployment to Iraq but, as a nationally dispersed cohort comprised of service members and military veterans at the time of long-term follow-up, were recruited individually for CSP#566. Sampling and recruitment for initial enrollment in Neurocognition Deployment Health Study and for CSP#566 core procedures are described elsewhere (Aslan et al., 2013; Vasterling et al., 2016).

Participants for the current study (Supplementary Figure S1) were recruited from 397 CSP#566 participants who had completed pre- and post-deployment neurocognitive testing, and who also scored ≥38, an established cutoff, on a performance validity index (Test of Memory Malingering [TOMM], trial 1) (O'Bryant, Engel, Kleiner, Vasterling, & Black, 2007) at previous assessments. In addition, CSP#566 participants were not considered eligible if their responses on self-report measures suggested invalid responding. Specifically, if their responses were unidirectional on self-report measures in which the pathological response varied in direction (e.g., choosing all "5"s on a Likert scale when "5" could indicate maximum distress on some items but minimum distress on others).

Of this pool, enrollment closed before full recruitment procedures could be completed on 36 participants who were sent an initial invitation, 33 could not be reached, and 13 declined participation, resulting in a sample of 315 participants.

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Participants in the current study ($n = 43$) were also excluded if, during the current assessment, they scored <38 on the TOMM, trial 1 ($n = 5$) or were determined by consensus discussion to be notably disengaged from study procedures (e.g., not looking at the computer screen for extended periods during task administration) ($n = 2$), if they reported deployment TBI history inconsistently across the post-deployment and long-term follow-up assessments ($n = 34$), completed no questionnaires ($n = 1$), or if they completed neurocognitive procedures >180 days after the phone interview ($n = 1$), yielding an analytic sample of $n = 272$.

Recruitment for the current study was conducted *via* phone after completion of the core (interview and questionnaire) CSP#566 procedures. Participants could opt to complete neurocognitive assessment procedures at a CSP#566 site (Boston, Seattle) ($n = 23$), or request that a CSP#566 examiner travel to conduct the assessment within the participant's home community ($n = 306$). Tests were administered in private, quiet settings whether at the study site or within the participant's community (e.g., rented hotel conference room).

Data Sources

Primary data from pre- and post-deployment assessments, occurring an average of 159.7 days ($SD = 139.1$ days; range = 2–589 days) before deployment and 100.3 days ($SD = 52.4$ days; range = 38–345 days) after return from deployment, were gathered in-person at military installations. TBI and PTSD data were derived from CSP#566 (long-term follow-up) phone interviews and mail surveys, occurring an average of 91.0 months ($SD = 11.4$ months; or 7.6 years, after the post-deployment assessment; range = 65.7–114.4 months). Details of the pre-deployment, post-deployment, and long-term follow-up assessments are described elsewhere (Vasterling, Proctor, Amoroso, Kane, Gacksetter, et al., 2006; Aslan et al., 2013). Deployment information was verified by Defense Manpower Data Center records.

The neurocognitive battery at long-term follow-up, administered an average of 34.2 days ($SD = 25.2$ days; range = 0–177 days) after the CSP#566 core assessment, included standardized tests of verbal-auditory learning and memory (Wechsler Memory Scale, 3rd Edition, Verbal Paired Associates I and II, respectively) (Wechsler, 1997), visual-spatial learning and memory (Wechsler Memory Scale Visual Reproductions, immediate and delayed recall, respectively) (Wechsler, 1945), reaction time efficiency (Automated Neuropsychological Assessment Metrics Simple Reaction Time) (Reeves, Kane, Elsmore, Winter, & Bleiberg, 2002), and sustained attention (Neurobehavioral Evaluation System, 3rd Edition., Continuous Performance Test) (Letz, Green, & Woodard, 1996). These tests were selected on the basis of previous Neurocognition Deployment Health Study findings indicating deployment-related performance differences (Vasterling, Proctor, Amoroso, Kane, Heeren, et al., 2006).

Variables extracted from these tests can be found in Table 1. All scoring was free of subjective judgment except for Visual Reproductions, which was scored according to set criteria. As with pre- and post-deployment assessments (Vasterling, Proctor, Amoroso, Kane, Heeren, et al., 2006), long-term follow-up reliability ratings, performed on 12% of randomly selected drawings by a second rater blinded to other study data, indicated high inter-rater reliability [intraclass correlations (ICC) = 0.94 for immediate recall; ICC = 0.95 for delayed recall].

The PTSD Checklist-Civilian version (PCL-C; Ruggiero, Del Ben, Scotti, & Rabalais, 2003), yielding a summary score of 17–85, was administered at all time-points and was used as a self-report measure of Diagnostic and Statistical Manual, 4th Edition text revision (DSM-IV-TR; American Psychiatric Association, 2000) PTSD symptom severity for the primary analyses. At long-term follow-up, the PCL-C summary score was highly correlated (Pearson r = 0.82; $p < .0001$) with the summary score of the Clinician Administered PTSD Scale (CAPS; Blake et al., 1995), a highly reliable structured interview considered to be a benchmark instrument for DSM-IV PTSD assessment (Weathers, Keane, & Davidson, 2001). The CAPS was administered only at long-term follow-up and, therefore, was not used in our longitudinal analyses. For the purposes of sample characterization only, the PCL-C was also used to determine probable PTSD cases at each assessment.

Congruent with other studies of Iraq deployment (Smith et al., 2008; Sundin et al., 2014), case definition was based on *DSM-IV-TR* symptom congruency and a cut-off of 50 on the

Table 1. Neuropsychological measures

Measure	Variable	Possible Range	Construct
WMS-III Verbal Paired Associates (VPA)			
VPA I	Total correct, trials 1–4	0–32	Verbal-auditory learning
VPA II	Total correct, delayed recall	0–8	Verbal-auditory memory
WMS Visual Reproductions (VR)			
VR immediate recall	Total accurate elements, cards A-C	0–14	Visual-spatial learning
VR delayed recall	Total accurate elements, cards A-C	0–14	Visual-spatial memory
ANAM Simple Reaction Time[a]	Throughput score	NA	Simple reaction time efficiency
NES3 Continuous Performance Test[a]	Total omission errors, log-transformed	NA	Sustained attention

WMS-III = Wechsler Memory Scale, 3rd edition. WMS = Wechsler Memory Scale. ANAM = Automated Neuropsychological Assessment Metric. NES3 = Neurobehavioral Evaluation System, 3rd Edition. NA = non-applicable. [a]Computer-assisted administration. Scores are raw scores unless otherwise indicated.

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summary score. Combat exposure was assessed using the Deployment Risk and Resilience Inventory (DRRI; Vogt, Proctor, King, King, & Vasterling, 2008) Combat Experiences Scale (CES), modified to include a frequency-based response scale and an item pertaining to convoy participation. Archived CES data, obtained at the post-deployment assessment, measured combat exposure between pre- and post-deployment. CSP#566 participants who deployed at least once following their post-deployment assessment completed the CES again, by telephone interview, in reference to their most recent deployment. CSP#566 participants who did not deploy between post-deployment and follow-up assessment were assigned a CES score of 0 for the post-deployment to follow-up time period.

TBI during the index deployment was ascertained by structured in-person interview during the post-deployment assessment. Of note, at the time of the index deployment (2003–2005), TBI events in the war-zone were not systematically captured within military medical records. In the context of time constraints associated with conduct of the study at military installations, and consistent with the early focus of the study on environmental hazards and stress, the post-deployment interview documented only TBI events associated with outright loss of consciousness (i.e., "knocked out") (Vasterling et al., 2012). This prioritization reflected attempts to capture those events with greater risk of adverse deployment-related clinical outcomes (Hoge et al., 2008; Luethcke et al., 2011).

Reflecting developing knowledge over the course of this multi-year longitudinal study, and long-term follow-up assessments conducted individually outside the context of military duties, lifetime history of TBI events associated with either (a) alteration of consciousness (explained as "dazed" or loss of memory for "what was happening during, immediately before, or immediately after the injury"), or (b) loss of consciousness, was documented at long-term follow-up (see Alosco et al., 2016 for further details). Long-term follow-up TBI interviews were conducted by a clinical psychologist using a structured phone interview.

Characteristics of the five most serious injuries for each participant were documented, including those experienced during the index deployment. Specifically, we used long-term follow-up report of TBI events with altered consciousness to supplement the post-deployment assessment report of TBI events with loss of consciousness during the index deployment. At both assessments, examiners clarified questions, as necessary, when participants were uncertain about their meaning. TBI classification required head injury or blast exposure ("injuries to your head or close exposures to explosive blasts"), with alteration or loss of consciousness. Each TBI event was categorized as mild or moderate-severe, based on commonly used categorizations for duration of loss of consciousness (mild: <30 min) and posttraumatic amnesia (mild: <24 hr).

Statistical Analyses

Data were analyzed using SAS v9.2 (SAS Institute Inc, Cary, NC) and Spotfire S + v8.2 (TIBCO Software Inc, Palo Alto, CA). Values for each missing PCL-C item, involving <5% of participants, were imputed case-wise, using the mean value of the PCL-C items completed during the relevant assessment episode for that person. The maximum number of missing items per individual case at each PCL-C administration was five (29% of 17 total items); no cases were missing > 50% of the items relevant to each PTSD symptom cluster (DSM-IV-TR Criteria B, C, D). Values for missing CES items, also involving < 5% of participants, were imputed case-wise using the mean value of the remaining completed items for that person. The maximum number of missing items per individual case at each CES administration was four (25% of 16 total items); three participants (1%) with multiple deployments were missing the entire CES on their most recent deployment.

To examine associations between the change in PTSD symptoms from pre- to post-deployment and post-deployment neurocognitive outcomes (hypothesis 1), we evaluated separate autoregressive linear regression models for each neurocognitive variable, adjusted for age at pre-deployment assessment. Age, pre-deployment ("autoregressive") values of post-deployment outcomes, pre- to post-deployment PCL-C difference scores, and the presence or absence of any TBI during the index deployment, were entered simultaneously; CES scores were added in a second step. Associations between change in PTSD symptoms from post-deployment to long-term follow-up with neurocognitive outcomes at long-term follow-up were modeled similarly, but with values relevant to the (a) time period of interest, and (b) presence or absence of any TBI event experienced between the post-deployment and long-term follow-up assessments.

To examine associations between pre-deployment neurocognitive test performances (hypothesis 2) and TBI (hypothesis 3) with post-deployment PTSD symptom outcomes, as measured by PCL-C summary scores, we evaluated two autoregressive linear regression models. Both models adjusted for age at pre-deployment assessment. Model 1 included simultaneous entry of Visual Reproductions, immediate recall (visual-spatial learning), Verbal Paired Associates I (verbal-auditory learning), Simple Reaction Time throughput (reaction time efficiency), and Continuous Performance Test log-transformed omission errors (sustained attention) as neurocognitive predictors, as well as the presence or absence of TBI during the index deployment; age and the pre-deployment PCL-C summary score were also included.

CES scores were added in a second step to account for environments (i.e., high combat intensity) hypothesized to increase risk of both TBI and PTSD. Model 2 was identical to model 1, but consistent with prior research (Marx, Doron-Lamarca, et al., 2009), Visual Reproductions delayed recall and Verbal Paired Associates II (indices of visual and verbal memory, respectively) were substituted for Visual Reproductions immediate recall and Verbal Paired Associates I, respectively, due to high intercorrelations between learning and memory indices. Associations between post-deployment neurocognitive performances and long-term PTSD symptom

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severity outcomes (CSP#566 assessment) were modeled similarly, but with values relevant to the time period of interest (hypotheses 2 and 3).

RESULTS

Participants

Sample characteristics are presented in Table 2. The majority of participants were men, Caucasian, and relatively young in age and without significant military experience at pre-deployment. Over time, an increasing number of participants obtained additional formal education, married, separated from military service, received military promotions, served in service support roles (with fewer in combat arms occupational specialties), deployed again, and were more likely to meet PTSD case definition (20% at long-term follow-up). TBI (Supplementary Table S1) was more prevalent between pre- and post-deployment assessment ($n = 73$) than between post-deployment assessment and long-term follow-up ($n = 60$). The majority of TBI events identified by participants as being the "most serious" were mild (89% of TBI events experienced between pre- and post-deployment assessment; > 83% of TBI events experienced between post-deployment assessment and long-term follow-up). Almost all (>98%) of the most recent events during each interval were post-acute (>3 months) at the time of neurocognitive testing. Participants also more frequently reported one event (*vs.* > 1 event) during both intervals.

Table 2. Participant characteristics across assessments ($n = 272$[a])

	Pre-deployment	Post-deployment	Pre- to post-deployment, *p* value	Long-term follow-up	Post-deployment to follow-up, *p* value
Age, mean (*SD*), years	26.1 (6.1)	27.8 (6.2)	0.0017	35.3 (6.1)	<.0001
Sex, No. (%)					
Men	256 (94.1)	—		—	
Women	16 (5.9)	—		—	
Race/ethnicity, No. (%)					
Caucasian	191 (70.2)	—		—	
African American	34 (12.5)	—		—	
Hispanic American	32 (11.8)	—		—	
Other	15 (5.5)	—		—	
Education, No. (%)			1.0		<.0001
High school or equivalent	182 (66.9)	182 (66.9)		58 (21.3)	
Part college	85 (31.3)	85 (31.3)		161 (59.2)	
College or greater	5 (1.8)	5 (1.8)		53 (19.5)	
Married, No. (%)	131 (48.3)	145 (53.5)	0.0035	181 (66.5)	0.0003
Army service, mean (*SD*), years	5.0 (5.1)	6.6 (5.2)	0.0002	11.3 (5.6)	<.0001
Duty status, No. (%)			<.0001		<.0001
Regular active duty	230 (84.6)	186 (68.6)		85 (31.3)	
Reservist	42 (15.4)	85 (31.4)		48 (17.7)	
Military veteran	0 (0)	0 (0)		139 (51.1)	
Most recent rank (using pay grade), No. (%)			<.0001		<.0001
Junior enlisted (E1 – E4)	185 (68.0)	124 (45.6)		56 (20.6)	
Non-commissioned officers (E5 –E9)	79 (29.0)	139 (51.1)		203 (74.6)	
Officers (commissioned or warrant)	8 (3.0)	9 (3.3)		13 (4.8)	
Most recent military occupation type, No. (%)			1.00		0.0004
Combat arms	130 (48.0)	130 (47.8)		113 (41.6)	
Combat support	36 (13.3)	36 (13.2)		39 (14.3)	
Service support	105 (38.8)	106 (39.0)		120 (44.1)	
Cumulative number of OEF/OIF deployments, No. (%)					
0	268 (98.5)	—		—	
1	4 (1.5)	267 (98.2)		107 (39.3)	
2	0 (0)	5 (1.8)		89 (32.7)	
3	0 (0)	0 (0)		64 (23.5)	
4	0 (0)	0 (0)		11 (4.0)	
5	0 (0)	0 (0)		1 (0.4)	
PTSD cases[b], No. (%)	13 (4.8)	19 (7.0)	0.34	54 (19.9)	<.0001
CES, mean (*SD*), summary score	—	16.7 (9.5)		7.5 (10.3)	<.0001

Data were tested with a McNemar test (categorical) or a paired *t* test (continuous). OEF = Operation Enduring Freedom. OIF = Operation Iraqi Freedom. PTSD = posttraumatic stress disorder. CES = Combat Experiences Scale. [a]Varies slightly across variables as a function of missing data. [b]PTSD cases were derived from the PTSD Checklist, civilian version.

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In aggregate, PTSD symptom severity, as measured by PCL-C summary scores, increased from pre- to post-deployment, and again from post-deployment to long-term follow-up (Supplementary Table S2). Neurocognitive performances either did not change significantly or improved over time (Supplementary Table S2). The analytic sample ($n = 272$) resembled the eligible participant pool ($n = 397$) on all sample characteristics (Supplementary Table S3).

Hypothesis 1: Association of PTSD Symptom Increases with Neurocognitive Performances

Examining neurocognitive performances as post-deployment outcomes (Table 3), fully adjusted linear regression models showed that increases in PTSD symptom severity from pre- to post-deployment were significantly associated with less proficient Verbal Paired Associates II and Simple Reaction Time throughput scores. In contrast, greater combat exposure was significantly associated with more proficient Simple Reaction Time throughput scores.

Fully adjusted models at long-term follow-up (Table 4) indicated that increases in PTSD symptom severity from post-deployment to long-term follow-up were significantly associated with less proficient scores on Visual Reproductions immediate and delayed recall, and Verbal Paired Associates II.

Associations between increases in PTSD symptom severity and neurocognitive outcomes were similar in models unadjusted for combat severity (data not shown).

Hypothesis 2: Association of Neurocognitive Performance with PTSD Symptom Severity as an Outcome

As shown in Table 5, fully adjusted linear regression models examining PTSD symptom severity as an outcome at post-deployment indicated an inverse relationship between performance on Visual Reproductions immediate recall at pre-deployment and post-deployment PTSD symptom severity.

Also shown in Table 5, fully adjusted models examining PTSD symptom severity as an outcome at long-term follow-up showed that more proficient post-deployment Visual Reproductions immediate recall and delayed recall scores were associated with less severe PTSD symptoms at long-term follow-up.

The patterns of association were similar in models unadjusted for combat severity (data not shown).

Hypothesis 3: Association of TBI with Neurocognitive Outcomes and PTSD Symptom Severity

TBI was not significantly associated with any neurocognitive outcomes at either post-deployment or long-term follow-up in both models, either unadjusted for combat severity (data not shown) or in fully adjusted models (Tables 3 and 4). As shown in Table 5, fully adjusted linear regression models inclusive of pre-deployment neurocognitive scores, as predictors of post-deployment PTSD symptom severity, indicated that the presence of TBI between pre- and post-deployment assessments was independently associated with more severe post-deployment PTSD symptoms, in both immediate and delayed recall models. Similarly, the presence of TBI between post-deployment assessment and long-term follow-up assessment was independently associated with more severe PTSD symptoms at long-term follow-up for both immediate and delayed recall models.

DISCUSSION

In this prospective study of U.S. Army soldiers who deployed to the Iraq War, we examined longitudinal relationships among PTSD symptom severity, TBI, and neurocognitive functioning over almost a decade, including assessments conducted before and after an index deployment, and a long-term follow-up assessment. Our findings, adjusted for age, education, race/ethnicity, military duty status, marital status, baseline values of the outcome variables, and combat severity, indicated a complex pattern of associations among PTSD symptom severity, learning and memory performance, and TBI that may contribute to sustaining adverse mental health outcomes over time. This study is novel in examining long-term longitudinal associations, inclusive of baseline data, among these deployment-relevant variable domains.

Associations between PTSD symptom severity and learning and memory performance in fully adjusted models (including adjustment for prior values of the outcome variables) suggest a possible bi-directional relationship between PTSD symptom severity and memory processes. Specifically, increases in PTSD symptom severity from pre- to post-deployment were associated with less proficient verbal memory; and, increases in PTSD symptom severity from post-deployment to long-term follow-up were associated with less proficient visual learning and memory in addition to less proficient verbal memory. Conversely, more proficient pre-deployment visual learning was associated with less severe post-deployment PTSD symptoms, with a similar pattern observed between post-deployment visual learning and memory performance and PTSD symptom severity at long-term follow-up.

A growing literature suggests that neurocognitive integrity, including learning and memory proficiency, may confer modest protection against PTSD development, or the severity of its expression, following trauma (Marx, Doron-Lamarca, et al., 2009; Parslow & Jorm, 2007). Our findings additionally suggest that variation in visual learning and memory integrity may moderate the long-term course of PTSD symptoms subsequent to its initial development. Although some conceptualizations of trauma memory suggest that semantic memory enhances the reconstruction of trauma narratives in a constructive manner (Brewin, Gregory, Lipton, & Burgess, 2010) and might predict that more proficient verbal memory, as compared with visual memory,

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Table 3. Final regression models for neuropsychological performance at post-deployment

	Visual Reproductions immediate recall		Visual Reproductions delayed recall		Verbal Paired Associates I		Verbal Paired Associates II		Simple Reaction Time efficiency[a]		Continuous Performance Test omissions[b]	
	Est (SE)	*p*	Est (SE)	*p*	Est (SE)	*p*	Est (SE)	*p*	Est (SE)	*p*	Est (SE)	*p*
Intercept	4.97 (0.74)	<.001	4.39 (0.79)	<.001	19.05 (2.26)	<.001	5.68 (0.63)	<.001	108.03 (16.14)	<.001	0.25 (0.16)	.11
Age at pre-deployment, years	0.02 (0.02)	.42	0.00 (0.02)	.93	–0.28 (0.06)	<.001	–0.07 (0.02)	<.001	–0.23 (0.29)	.43	0.00 (0.01)	.39
Education[c]												
Part college	0.13 (0.23)	.56	0.61 (0.25)	.02	2.36 (0.76)	.002	0.56 (0.19)	.004	–2.26 (3.62)	.53	–0.07 (0.06)	.27
College or higher	–0.57 (0.78)	.47	0.52 (0.86)	.55	1.90 (2.58)	.46	1.27 (0.65)	.05	12.07 (12.32)	.33	0.41 (0.21)	.05
Race/ethnicity[d]												
African American	–0.53 (0.33)	.11	–0.60 (0.36)	.10	–0.71 (1.08)	.51	–0.06 (0.27)	.84	–2.59 (5.20)	.62	0.03 (0.09)	.78
Hispanic	–0.59 (0.33)	.07	–0.36 (0.37)	.33	–0.69 (1.09)	.52	–0.08 (0.27)	.77	–4.83 (5.24)	.36	0.03 (0.09)	.78
Other	0.21 (0.45)	.63	0.25 (0.50)	.62	.34 (1.49)	.82	0.28 (0.38)	.45	–10.02 (7.17)	.16	0.07 (0.12)	.55
Married[e]	–0.06 (0.22)	.78	–0.04 (0.24)	.87	0.94 (0.72)	.19	0.12 (0.18)	.52	1.88 (3.44)	.58	0.00 (0.06)	1.00
Reservist[f]	–0.01 (0.24)	.95	–0.51 (0.27)	.06	–0.71 (0.79)	.37	–0.33 (0.20)	.09	3.70 (3.78)	.33	0.01 (0.07)	.88
Autoregressor[g]	0.38 (0.05)	<.001	0.48 (0.05)	<.001	0.56 (0.05)	<.001	0.47 (0.05)	<.001	0.42 (0.06)	<.001	0.21 (0.06)	<.001
PCL-C difference score[h]	–0.01 (0.01)	.24	0.00 (0.01)	.83	–0.04 (0.03)	.18	–0.02 (.01)	.03	–0.28 (0.14)	.05	0.00 (0.00)	.36
TBI present	–0.21 (0.25)	.40	–0.35 (0.28)	.21	0.28 (0.83)	.73	0.00 (0.21)	1.00	3.44 (3.97)	.39	0.07 (0.07)	.33
CES, post-deployment score	0.02 (0.01)	.11	0.01 (0.01)	.72	–0.04 (0.04)	.33	–0.01 (0.01)	.30	0.39 (0.19)	.04	0.00 (0.00)	.53

Higher neuropsychological scores indicate more proficient performance except for Continuous Performance Test omissions. All demographic and military variables pertain to post-deployment values unless otherwise indicated. R^2 values = 0.21, 0.27, 0.40, 0.41, 0.22, 0.07 for Visual Reproductions immediate recall, Visual Reproductions delayed recall, Verbal Paired Associates I, Verbal Paired Associates II, Simple Reaction Time efficiency, and Continuous Performance Test omissions, respectively. PTSD = posttraumatic stress disorder. TBI = traumatic brain injury. Est (SE) = estimate (standard error). PCL-C = PTSD Checklist, civilian version. CES = Combat Experiences Scale. [a]Throughput scores. [b]Log-transformed. [c]Reference = high school or equivalent. [d]Reference = Caucasian. [e]Reference = not married. [f]Reference = active duty. [g]Denotes the pre-deployment value of the corresponding neuropsychological outcome variable. [h]Calculated as (post-deployment PCL-C score – pre-deployment PCL-C score).

Table 4. Final regression models for neuropsychological performance at long-term follow-up

	Visual Reproductions immediate recall		Visual Reproductions delayed recall		Verbal Paired Associates I		Verbal Paired Associates II		Simple Reaction Time efficiency[a]		Continuous Performance Test omissions[b]	
	Est (SE)	*p*	Est (SE)	*p*	Est (SE)	*p*	Est (SE)	*p*	Est (SE)	*p*	Est (SE)	*p*
Intercept	7.36 (0.84)	<.001	5.34 (0.93)	<.001	13.70 (2.48)	<.001	4.79 (0.69)	<.001	188.81 (21.30)	<.001	−0.21 (0.18)	.24
Age at pre-deployment, years	−0.04 (0.02)	.05	−0.03 (0.02)	.23	−0.05 (0.06)	.39	−0.02 (0.01)	.12	−0.64 (0.38)	.09	0.01 (0.01)	.17
Education[c]												
Part college	0.32 (0.27)	.24	0.14 (0.31)	.64	0.03 (0.78)	.97	0.07 (0.21)	.74	−4.67 (5.47)	.39	0.10 (0.07)	.14
College or higher	0.56 (0.34)	.09	0.02 (0.38)	.95	−0.46 (0.99)	.65	−0.20 (0.26)	.43	3.86 (6.87)	.57	0.10 (0.09)	.24
Race/ethnicity[d]												
African American	−0.31 (0.32)	.34	−0.33 (0.36)	.37	−1.40 (0.93)	.13	−0.25 (0.24)	.31	−1.76 (6.52)	.79	−0.01 (0.08)	.88
Hispanic	−0.11 (0.33)	.75	−0.29 (0.38)	.44	0.07 (0.95)	.94	−0.02 (0.25)	.93	−5.91 (6.67)	.38	0.00 (0.08)	.99
Other	0.36 (0.45)	.42	0.05 (0.51)	.93	1.27 (1.32)	.34	−0.24 (0.35)	.49	3.81 (9.25)	.68	0.00 (0.12)	.97
Married[e]	−0.01 (0.24)	.95	0.20 (0.27)	.46	0.43 (0.69)	.54	0.09 (0.18)	.63	3.14 (4.80)	.51	−0.07 (0.06)	.28
Duty status[f]												
Reservist	0.10 (0.32)	.76	0.33 (0.37)	.37	0.57 (0.93)	.54	0.33 (0.25)	.18	−11.63 (6.52)	.08	0.13 (0.08)	.12
Military veteran	−0.52 (0.26)	.05	0.03 (0.30)	.93	−0.20 (0.76)	.79	0.23 (0.20)	.24	−5.84 (5.30)	.27	0.03 (0.07)	.61
Autoregressor[g]	0.36 (0.06)	<.001	0.48 (0.06)	<.001	0.55 (0.05)	<.001	0.45 (0.05)	<.001	0.40 (0.07)	<.001	0.14 (0.06)	.02
PCL-C difference score[h]	−0.02 (0.01)	.03	−0.03 (0.01)	.001	−0.02 (0.02)	.25	−0.01 (0.01)	0.03	−0.05 (0.14)	.74	0.00 (0.00)	.07
TBI present	0.11 (0.27)	.69	0.23 (0.31)	.46	0.49 (0.78)	.53	0.22 (0.21)	.29	−4.58 (5.47)	.40	0.08 (0.07)	.28
CES, post-deployment score	−0.01 (0.01)	.41	0.00 (0.01)	.87	−0.03 (0.03)	.43	−0.01 (0.01)	.52	0.03 (0.23)	.91	0.00 (0.00)	.21

Higher neuropsychological scores indicate more proficient performance except for Continuous Performance Test omissions. All demographic and military variables pertain to long-term follow-up values unless otherwise indicated. R^2 values = 0.22, 0.31, 0.42, 0.33, 0.17, 0.08 for Visual Reproductions immediate recall, Visual Reproductions delayed recall, Verbal Paired Associates I, Verbal Paired Associates II, Simple Reaction Time efficiency, and Continuous Performance Test omissions, respectively. PTSD = posttraumatic stress disorder. TBI = traumatic brain injury. Est (SE) = estimate (standard error). PCL-C = PTSD Checklist, civilian version. CES = Combat Experiences Scale. [a]Throughput scores. [b]Log-transformed. [c]Reference = high school or equivalent. [d]Reference = Caucasian. [e]Reference = not married. [f]Reference = active duty. [g]Denotes the post-deployment value of the corresponding neuropsychological outcome variable. [h]Calculated as (long-term follow-up PCL-C score – post-deployment PCL-C score).

Table 5. PCL-C outcomes at post-deployment and long-term follow-up, examining immediate (A) and delayed (B) recall scores separately

A. Immediate recall (IR) model					
	Post-deployment			Long-term follow-up	
	$R^2 = 0.27$			$R^2 = 0.32$	
	Est (SE)	*p*		Est (SE)	*p*
Intercept	19.55 (7.47)	.01	Intercept	27.46 (10.42)	.01
Age at pre-deployment, years	0.13 (0.11)	.26	Age at pre-deployment, years	0.06 (0.16)	.72
Education, post-deployment[a]			Education, follow-up[a]		
Part college	1.20 (1.43)	.40	Part college	3.85 (2.23)	.09
College or higher	7.25 (4.79)	.13	College or higher	−2.43 (2.81)	.39
Race/ethnicity[b]			Race/ethnicity[b]		
African American	0.08 (2.04)	.97	African American	2.83 (2.66)	.29
Hispanic	−0.17 (2.05)	.94	Hispanic	−0.59 (2.71)	.83
Other	−2.32 (2.79)	.41	Other	−5.07 (3.74)	.18
Married, post-deployment[c]	0.12 (1.34)	.93	Married, follow-up[c]	1.00 (1.98)	.62
Duty status, post-deployment[d]			Duty status, follow-up[d]		
Reservist	3.69 (1.46)	.01	Reservist	−0.24 (2.67)	.93
			Military veteran	10.02 (2.11)	<.001
PCL-C score, pre-deployment	0.43 (0.06)	<.001	PCL-C score, post-deployment	0.42 (0.07)	<.001
VPA I score, pre-deployment	0.10 (0.10)	.30	VPA-I score, post-deployment	−0.09 (0.13)	.49
VR IR score, pre-deployment	−0.64 (0.32)	.05	VR IR score, post-deployment	−1.15 (0.47)	.02
CPT omissions[e], pre-deployment	−0.10 (1.42)	.94	CPT omissions[e], post-deployment	0.90 (1.87)	.63
SRT efficiency[f], pre-deployment	−0.04 (0.03)	.17	SRT efficiency[f], post-deployment	−0.04 (0.03)	.23
TBI present[g]	6.47 (1.50)	<.001	TBI present[h]	5.76 (2.24)	.01
CES score, post-deployment	0.12 (0.07)	.09	CES score, post-deployment	0.31 (0.09)	.001
B. Delayed recall (DR) model					
	Post-deployment			Long-term follow-up	
	$R^2 = 0.27$			$R^2 = 0.32$	
	Est (SE)	*p*		Est (SE)	*p*
Intercept	19.00 (7.54)	.01	Intercept	23.26 (10.52)	.03
Age at pre-deployment, years	0.12 (0.12)	.32	Age at pre-deployment, years	0.09 (0.16)	.57
Education, post-deployment[a]			Education, follow-up[a]		
Part college	1.01 (1.43)	.48	Part college	3.73 (2.23)	.10
College or higher	7.02 (4.80)	.14	College or higher	−2.10 (2.81)	.45
Race/ethnicity[b]			Race/ethnicity[b]		
African American	0.18 (2.04)	.93	African American	2.77 (2.67)	.30
Hispanic	−0.27 (2.05)	.89	Hispanic	0.04 (2.74)	.99
Other	−2.12 (2.81)	.45	Other	−4.90 (3.76)	.19
Married, post-deployment[c]	0.17 (1.34)	.90	Married, follow-up[c]	0.49 (1.98)	.80
Duty status, post-deployment[d]			Duty status, follow-up[d]		
Reservist	3.83 (1.46)	.01	Reservist	−1.13 (2.70)	.68
			Military veteran	8.94 (2.16)	<.001
PCL-C score, pre-deployment	0.43 (0.06)	<.001	PCL-C score, post-deployment	0.43 (0.07)	<.001
VPA II score, pre-deployment	0.12 (0.34)	.71	VPA II score, post-deployment	0.04 (0.53)	.93
VR DR score, pre-deployment	−0.58 (0.31)	.06	VR DR score, post-deployment	−1.06 (0.43)	.01
CPT omissions[e], pre-deployment	−0.31 (1.41)	.82	CPT omissions[e], post-deployment	1.01 (1.88)	.59
SRT efficiency[f], pre-deployment	−0.03 (0.03)	.23	SRT efficiency[f], post-deployment	−0.04 (0.03)	.23
TBI present[g]	6.51 (1.50)	<.001	TBI present[h]	5.86 (2.25)	.01
CES score, post-deployment	0.14 (0.07)	.07	CES score, post-deployment	0.30 (0.09)	.002

Higher scores on neuropsychological tests indicate more proficient performance except for Continuous Performance Test omissions. PCL-C = PTSD Checklist, civilian version. Est (SE) = estimate (standard error). VPA = Verbal Paired Associates. VR = Visual Reproductions. IR = immediate recall. DR = delayed recall. SRT = Simple Reaction Time. CPT = Continuous Performance Test. TBI = traumatic brain injury. CES = Combat Experiences Scale. [a]Reference = high school or equivalent. [b]Reference = Caucasian. [c]Reference = not married. [d]Reference = active duty. [e]Log-transformed. [f]Throughput scores. [g]Pre-deployment to post-deployment assessment. [h]Post-deployment to long-term follow-up.

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would be more strongly associated with subsequent PTSD severity, it may also be that the ability to form a visual image facilitates rehearsal and habituation to the perceptual aspects of a trauma event, as well as their integration into a coherent narrative (Brewin et al., 2010).

This notion is supported by studies indicating that visual imagery can be more effective than verbal processing in reducing anxiety (Holmes & Mathews, 2005) and by findings showing that decreased visual input reduces the recollection of autobiographical events (Rubin, Burt, & Fifeld, 2003). Moreover, as suggested by Gilbertson et al. (2007), it may be that small hippocampal volume, possibly reflected in our study by relatively less proficient performance on visual learning and memory tasks, increases risk of greater subsequent PTSD severity through the failure to support visually-mediated extinction of conditioned emotional responses.

Consistent with conceptualizations of PTSD as a biopsychosocial disorder involving alterations in neural functioning (Pitman et al., 2012), our findings also suggest that PTSD may subtly erode these potentially resilience-enhancing cognitive resources (i.e., learning and memory) as PTSD symptoms increase in severity. For example, neuroendocrine dysfunction, including dysregulation of glucocorticoids, is thought to be a core neurobiological feature of PTSD. Relevant to our findings, there are well-documented links between glucocorticoids and memory (Wingenfeld & Wolf, 2011). Our findings taken as a whole suggest a bi-directional relationship between memory and PTSD symptom severity, a relationship that we detected even in the absence of clinically significant (>15%) decline in learning and memory.

Also consistent with our previous findings using overlapping samples (Marx, Brailey, et al., 2009; Vasterling, Proctor, Amoroso, Kane, Heeren, et al., 2006), we found that more extensive combat exposure was modestly associated with greater efficiency on a reaction time test (Simple Reaction Time) at post-deployment assessment. This finding can be interpreted as part of a broader unresolved stress response in which organisms prepare for survival in life-threatening contexts such as combat, in part *via* heightened arousal and in part by focusing attention more narrowly. Simple Reaction Time, which requires speeded responses to simple recurrent targets, could be hypothesized to capture this evolutionarily adaptive response. Conversely, increases in PTSD symptom severity from pre- to post-deployment were associated with less efficient reaction time, suggesting that the exposure to potential threat is dissociable from post-traumatic emotional responses in their effects on reaction time.

Regarding TBI, we found that the presence of TBI (predominantly mild in our sample) during each assessment interval (i.e., pre- to post-deployment; post-deployment to long-term follow-up) was associated with more severe PTSD symptoms at the conclusion of the interval. It has been hypothesized that the psychological trauma associated with deployment TBI, and the warzone context in which it occurs, accounts for the increased risk of PTSD in warzone veterans with history of mild TBI (Hoge et al., 2008). In contrast, our findings, which were adjusted for combat severity, suggest that mild TBI contributes to PTSD symptom expression independently of combat stress and are consistent with Yurgil et al. (2014), who found that deployment TBI predicted postdeployment PTSD after adjusting for combat severity.

Additionally, TBI events in our study were not limited to deployment, particularly during the post-deployment to long-term follow-up period. Consistent with a longitudinal study of civilians indicating that mild TBI experienced outside the context of combat was associated with poorer PTSD outcomes, both within the year after the injury (Bryant et al., 2010) and over 6 years later (Bryant et al., 2015), our findings indicate that increased risk of PTSD following mild TBI in military populations is not restricted to deployment TBI. Other potential mechanisms explaining the association between TBI and PTSD, including increased disease burden *via* undocumented TBI co-morbidities (e.g., associated orthopedic injury) and acute TBI-related mental status changes affecting the formation of trauma memories in a manner precluding optimal subsequent processing of the memories (Vasterling, Verfaellie, & Sullivan, 2009), could not be tested by our study design.

TBI was not significantly associated with any measure of neurocognitive functioning during any time period, either before (data not shown) or after adjustment for combat severity. This finding, in the context of predominantly mild TBI experienced over three months before pre-deployment testing and over a year before long-term follow-up testing in most of our sample, is consistent with meta-analytic research suggesting that acute neurocognitive decrements following mild TBI tend to resolve within 90 days in most people (Karr et al., 2014). Recent studies, however, suggest that white matter abnormalities may mediate the relationship of mild deployment TBI to neurocognitive performance (Clark et al., 2016; Hayes, Miller, Lafleche, Salat, & Verfaellie, 2015). Thus, it remains unclear whether our results and other findings relying on aggregate data potentially mask poor performance in subgroups for whom deficits do not resolve as quickly as in the majority of those experiencing mild TBI (Belanger, Curtiss, Demery, Lebowitz, & Vanderploeg, 2005; Pertab, James, & Bigler, 2009).

Our findings should be interpreted in the context of the study's methodological strengths and limitations. Although our TBI interview administered at long-term follow-up has been shown to have high inter-rater reliability and was conducted by doctoral level clinicians (Alosco et al., 2016), retrospective report of TBI events may be subject to memory and other reporting biases. To minimize this possibility, we used data from our post-deployment TBI interview to document TBI with loss of consciousness and excluded participants who reported deployment interval TBI inconsistently across post-deployment and long-term follow-up assessments. Because we did not capture TBI with altered consciousness at the post-deployment assessment, however, we relied on long-term follow-up accounts of these events to supplement our post-deployment assessment of TBI with loss of consciousness.

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Findings should also be interpreted in the context of the TBI events captured. Although most were mild, a small proportion (11.0% occurring between pre- and post-deployment assessments; 16.7% of those occurring between post-deployment and long-term follow-up assessments) were categorized as greater than mild, thereby introducing some heterogeneity of severity. We additionally did not capture the mechanism of injury (e.g., blast, blunt trauma, etc.), although there is not yet clear evidence that mechanism of injury strongly influences neuropsychological outcomes in military populations (Belanger, Kretzmer, Yoash-Gantz, Pickett, & Tupler, 2009; Mac Donald et al., 2014). Finally, we examined non-deployment-related TBI in addition to deployment TBI. The inclusion of both deployment and non-deployment-related TBI, however, enhances the generalization of findings within the military and military veteran population, a population at risk for TBI events in civilian as well as military contexts (Armistead-Jehle, Soble, Cooper, & Belanger, 2017; Regasa et al., 2016).

We assessed a relatively limited range of neurocognitive functions and could not feasibly capture other neurobiologically relevant data (e.g., neuroimaging, biological assays), but our measures were selected based on their sensitivity to deployment-related effects and included a performance based validity index as an eligibility criterion, a feature that has been only infrequently included in studies of PTSD and neurocognition. Furthermore, our use of performance-based tests individually administered in person, in the context of a longitudinal study of a nationally-dispersed sample, is a rare methodological strength. PTSD symptom severity was measured *via* a face valid self-report instrument (i.e., PCL-C), but the PCL-C, designed to measure symptom severity, has strong psychometric properties (Wilkins, Lang, & Norman, 2011) and showed strong correlations with CAPS symptom severity scores when analyzed as a severity measure. Notably, a major methodological strength of our study was our ability to account for prior values of both PTSD symptom and neuropsychological outcomes, including pre-deployments levels.

It is possible that conditions that are commonly co-morbid to PTSD and/or TBI but that were not captured in this study (e.g., depression, chronic pain) contributed to neuropsychological decrements. Of note, there were only a small number of women in the sample, thereby precluding examination of any gender effects. Finally, because a comparison sample of non-deployed soldiers was no longer plausible within the NDHS cohort, we were unable to examine the longer-term effects of deployment (*vs*. non-deployment).

In conclusion, although our sample displayed relatively robust neural health, as indicated by neurocognitive performances, findings indicate specific risk factors for relative neurocognitive performance decrements and suggest that the constellation of PTSD, TBI, and relative neurocognitive decrements may contribute, *via* their longitudinal associations, to sustaining emotional and neurocognitive symptoms over time. More generally, these novel findings help elucidate potential bi-directional relationships between neurocognition, as a behavioral and mechanistically relevant indicator of neural health, and PTSD in trauma-exposed populations and highlight neurocognition as both a predictor and outcome of emotional distress following trauma.

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Supplementary material

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