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Can mild traumatic brain injury alter cognition chronically? A LIMBIC-CENC multicenter study

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Abstract

Objective: While outcome from mild traumatic brain injury (mTBI) is generally favorable, concern remains over potential negative long-term effects, including impaired cognition. This study examined the link between cognitive performance and remote mTBIs within the Long-term Impact of Military-relevant Brain Injury Consortium-Chronic Effects of Neurotrauma Consortium (LIMBIC-CENC) multicenter, observational study of Veterans and Service Members (SMs) with combat exposure.

Method: Baseline data of the participants passing all cognitive performance validity tests (n=1,310) were used to conduct cross-sectional analysis. Using multivariable regression models that adjusted for covariates, including age and estimated pre-exposure intellectual function, positive mTBI history groups, 1–2 lifetime mTBIs (non-repetitive, n=614) and 3+ lifetime mTBIs (repetitive; n=440) were compared to TBI negative controls (n=256) on each of seven cognitive domains computed by averaging Z-scores of prespecified component tests. Significance levels were adjusted for multiple comparisons.

Results: Neither of the mTBI positive groups differed from the mTBI negative control group on any of the cognitive domains in multivariable analyses. Findings were also consistently negative

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across sensitivity analyses (e.g., mTBIs as a continuous variable, number of blast-related mTBIs, or years since first and last mTBI).

Conclusions: Our findings demonstrate that the average Veteran or SM who experienced one or more mTBIs does not have post-acute objective cognitive deficits due to mTBIs alone. A holistic healthcare approach including comorbidity assessment is indicated for patients reporting chronic cognitive difficulties after mTBI(s), and strategies for addressing misattribution may be beneficial. Future study is recommended with longitudinal designs to assess within-subjects decline from potential neurodegeneration.

Keywords

traumatic brain injury; concussion; cognition; neuropsychological testing; military

BACKGROUND

Traumatic brain injury (TBI) is defined as a traumatically induced structural injury and/or physiological disruption of brain function as a result of an external force that is indicated by new onset or worsening of at least one of the following clinical signs immediately following the event: loss of consciousness (LOC), memory gap consistent with post-traumatic amnesia (PTA), alteration of mental state (e.g., dazed, confused), or neurological deficits (American Congress of Rehabilitation Medicine, 1993; Work Group, 2021). Expert consensus definitions by the American Congress of Rehabilitation Medicine (ACRM) and the Departments of Veterans Affairs and Defense working group on a common definition further classify TBI severity as mild, moderate, or severe, with classification as mild if LOC does not exceed 30 minutes, initial Glasgow Coma Score is not below 13, PTA does not exceed 24 hours, and there is no evidence of traumatic intracranial hemorrhage on clinical imaging (American Congress of Rehabilitation Medicine, 1993; Work Group, 2021). Mild TBI (mTBI), often termed concussion, is by far the most common severity category in both civilian and military populations. Since 2000, more than 430,000 United States (U.S.) Service Members (SMs) have sustained a documented TBI, with the vast majority (>80%) of cases categorized as mTBI (TBI Center of Excellence, 2021). The Veterans Health Administration conducts mTBI screening on all returning Post-9/11 Veterans, but only those reporting active symptoms receive a comprehensive TBI evaluation. Therefore, actual case prevalence is likely higher due to commonly occurring, undocumented mTBI history (Donnelly et al., 2011)

Cognitive dysfunction is a clinical hallmark of TBI, manifesting behaviorally, symptomatically, and/or as reduced performance on objective cognitive tests. After severe TBI, acute neurocognitive dysfunction is usually pronounced and obvious with a period of frank disorientation and confusion or worse. Objective evidence of reduced cognition is also commonly measurable within the first several weeks after mTBI (Karr et al., 2014). Over time, cognitive performance normally improves to varying degrees. In severe TBI, full recovery is atypical and chronically-reduced cognition is common (Dikmen et al., 2009; J. Ponsford et al., 2008; Ruttan et al., 2008); whereas with mTBI, most patients have excellent, if not full, recoveries within several days to months. In general, objective, late cognitive deficits after mTBI have been elusive to document at the group level, with

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multiple, meta-analytic reviews concluding insufficient evidence for deleterious effects of mTBI on objective cognitive assessment beyond the first few months post-injury (Belanger et al., 2005; Binder et al., 1997; Frencham et al., 2005; Karr et al., 2014; O'Neil et al., 2014; Rohling et al., 2011; Schretlen & Shapiro, 2003).

Nevertheless, 20% or more of patients with mTBI experience persistent post-concussion symptoms (PPCS) (Lagacé-Legendre et al., 2021), previously referred to as 'post-concussive syndrome' (Brenner et al., 2009). PPCS typically include cognitive symptoms, such as decreased concentration, memory, and processing speed, in addition to somatic and emotional symptoms, such as headache, dizziness, disordered sleep, fatigue, irritability, increased arousal, and sensitivity to light and sound (Brenner et al., 2009; Stein & McAllister, 2009). PPCS are especially common among U.S. Veterans and SMs who sustained mTBI in the post-911 wars, including Operation Enduring Freedom (OEF), Operation Iraqi Freedom (OIF), and Operation New Dawn (OND) (Cifu et al., 2013; Hendricks et al., 2013; Taylor et al., 2012). Despite the common occurrence of chronic cognitive subjective symptomology after mTBI, extant research shows a lack of a consistent relationship with cognitive performance on formal neuropsychological examination, including samples of military personnel (Mac Donald et al., 2017). The Veterans Affairs (VA) /Department of Defense (DoD) clinical practice guideline (Work Group, 2021), the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5), and other standardized guides, make a distinction between mTBI as an injurious historical event and PPCS with or without mild cognitive disorder (Cnossen et al., 2017; Iverson, 2019).

Despite the lack of convincing objective evidence that mTBI chronically alters cognitive performance, there remains justifiable concern that mTBI may lead to not only PPCS, but also chronic neurocognitive impairment. Many argue that TBI should be considered an evolving, chronic condition, even if initial severity was mild (Wilson et al., 2017). One explanation for negative findings in most studies may be the subtle nature of cognitive performance effects that may be present in only a small subset of patients. As studies examining control group comparators do not consider premorbid cognitive performance, they may fail to detect mild within-subject reductions. Another confounder in detecting cognitive impairment in the chronic stage of mTBI may be that other common comorbidities adversely impact performance on tests of cognition. These include psychiatric disorders (Vasterling et al. 2012), sleep abnormalities (Anderson & Jordan, 2021), and pain (Khalid & Tubbs, 2017). Sleep is an especially important variable to consider, given its known impact on cognitive performance (Fortier-Brochu et al., 2012), and the prevalence of insomnia, sleep apnea, and other sleep disorders among those with a history of mTBI (J. L. Ponsford et al., 2013; Schreiber et al., 2008). Comorbid posttraumatic stress disorder (PTSD) and chronic pain are also important considerations as many symptoms and deficits that accompany PTSD and chronic pain are non-specific and overlap with mTBI (Iverson, 2006; Otis et al., 2011; Porter et al., 2018). Additionally suboptimal effort and secondary gain may accompany self-reports of cognitive difficulty (Armistead-Jehle et al., 2016).

There is emerging evidence that repeated mTBI may confer additional risk for both persisting symptoms and cognitive compromise. In civilians, repetitive mTBIs often encountered in sports, including football, boxing, and soccer (Guskiewicz et al., 2003;

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Safinia et al., 2016), may be related to impairment over longer time periods, (Guskiewicz et al., 2003; Miller et al., 2013), or serve as risk factors for developing other conditions, including neurodegenerative disorders (Vincent et al., 2014). A recent animal study demonstrated that repetitive TBIs can result in worse and more persistent neurological deficits compared to a single TBI (Bachstetter et al., 2020). A meta-analysis concluded that multiple concussions appear to be a risk factor for cognitive impairment in some individuals (Manley et al., 2017). However, the literature remains inconclusive, as many other studies have failed to demonstrate an effect of repeated mTBI on objective cognitive performance (Belanger et al., 2010) (Cooper et al., 2018; Macciocchi et al., 2001). Another factor specific to military populations with mixed research evidence is the concern that blast-related mTBI has more enduring long-term effects on cognition compared to blunt mTBI (Belanger et al., 2009; Martindale et al., 2020).

Taken together, there is inconclusive research regarding the risk of chronic, neurocognitive decrements after a single mTBI or even repeated mTBIs. The Long-term Impact of Military-relevant Brain Injury Consortium (LIMBIC)-Chronic Effects of Neurotrauma Consortium's (LIMBIC-CENC) multicenter, prospective longitudinal study (PLS) was designed to address this critical research gap and to improve understanding of the long-term effects of mTBI within the military and veteran populations (Walker et al., 2016; Walker, Hirsch, et al., 2018). The current study utilized the baseline (at enrollment) evaluations from the large LIMBIC-CENC PLS dataset. Our specific aim was to determine the amount of variance explained by mTBI history alone on current, objective, cognitive performance in domains that have been demonstrated to be impacted in both civilian and military-related mild TBI including episodic and working memory, attention, processing speed, executive functioning and fine motor dexterity (Barker-Collo et al., 2015; Storzbach et al., 2015; Wilde et al., 2010). The main hypothesis was, compared to those reporting totally negative mTBI histories, those with three or more lifetime mTBIs (repetitive mTBI) have lower performance on these cognitive domains when adjusting for comorbidities and other potential contributing factors. Other aspects of mTBI history that our analysis considered were the total number of mTBIs measured continuously, the mTBI(s) mechanism (blast versus blunt), and elapsed time between mTBI event(s) and time of testing.

METHODS

Design:

This cross-sectional study analyzed data collected at the enrollment visit for the ongoing LIMBIC-CENC multicenter PLS. Details of the LIMBIC-CENC PLS objectives, recruitment processes, eligibility criteria, and overall methods have been previously described (Sickinger et al., 2018; Walker et al., 2016; Walker, Hirsch, et al., 2018). Briefly, the PLS is a longitudinal, observational study that has established a large multicenter cohort of cohort of current and former U.S. SMs with combat exposure and continues to enroll new participants at eleven geographically dispersed sites. While most participants experienced one or more lifetime mTBIs, slightly less than 20% report completely negative lifetime TBI histories. The overall study objective is to answer questions about the long-term effects of mTBI including the relationship to other factors and sequelae of combat exposure. At the

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baseline visit after enrollment, all participants underwent comprehensive assessment that included an extensive neuropsychological test battery, symptom inventories, and biometrics. Participants were primarily recruited through mass mailings and non-paid advertisements. All individuals 18 years of age or older with a history of combat exposure are eligible to participate in this study. The only exclusions were a history of moderate to severe TBI or major neurologic or psychiatric disorder, such as stroke or schizophrenia, with significant decrease in functional status. Common mental health comorbidities, such as PTSD and depression, were permitted. The parent study, including the database registry and all secondary analyses, was approved by the local Institutional Review Boards at each of the PLS enrollment sites. All participants provide written consent prior to any study procedures.

Sample selection

At the time of this data extraction, 1,551 participants had enrolled in the PLS and completed baseline assessments. For the current analyses, only data collected at baseline assessment were utilized, and participants who failed any of the three tests of performance validity described further below were excluded.

Lifetime Mild TBI history:

Clinical diagnosis of all lifetime mTBI(s) was obtained through a rigorous, standardized process. Each participant's potential concussive events (PCEs) were cataloged using a modified version of the Ohio State University TBI Identification (OSU TBI-ID) (Corrigan & Bogner, 2007). Each PCE was then assessed via a validated retrospective Concussion Diagnostic Interview, yielding a preliminary algorithm-generated TBI diagnosis (No mTBI, mTBI with PTA, or mTBI without PTA) (Walker et al., 2015). Every algorithm rating was then reviewed, checked against available medical records, and vetted with a centralized, expert committee to yield a final determination that adhered to the VA/DoD common definition of mTBI (Management of Concussion/mTBI Working Group, 2009), which is also consistent with the American Congress of Rehabilitation Medicine definition of mTBI (American Congress of Rehabilitation Medicine, 1993). From this TBI categorization data, positive lifetime mTBI histories were subclassified for these analyses as either 1) non-TBI control, 2) 1–2 lifetime mTBIs (non-repetitive mTBI), or 3) 3+ lifetime mTBIs (repetitive mTBI). The classification for non-repetitive versus repetitive mTBI was based on evidence from prior LIMBIC-CENC PLS studies showing differences between these groups in postural stability (Walker, Nowak, et al., 2018) and brain-based biomarkers (Kenney et al., 2018), and to achieve approximately equal group sizes for better statistical power. For planned sensitivity analyses, we alternatively replaced the mTBI frequency categories by its continuous version, the total number of lifetime mTBIs, and we separately analyzed the total number of lifetime mTBIs that were of blast-related mechanism. We also considered years since first and last mTBI as covariates.

Years since index event: For mTBI positive participants, the self-described worst mTBI served as the index event unless there were zero lifetime mTBIs (or all mTBIs were before any military combat) in which case the self-identified worst PCE during a combat deployment was used for a control comparison.

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Cognitive Performance Testing:

The extensive LIMBIC-CENC cognitive test battery includes a spectrum of traditional neuropsychological tests and the recently developed computerized NIH Toolbox Cognition Battery (NIHTB-CB). All instruments used are recommended as part of the NIH Common Data Elements for mTBI (Hicks et al., 2013). All neuropsychology test administrators were trained to conduct each assessment following the standardized procedures established by the test developer prior to study enrollment. Administrators were required to submit a video recording of themselves conducting the neuropsychology battery on a test subject to assess fidelity of assessment implementation. Regular auditing was performed on all neuropsychology data to ensure there were no transcription errors from case report form to database entry and to detect and remedy if needed any study wide or site-specific scoring drift.

To minimize spurious findings, we utilized a hypothesis-driven approach to preselect a comprehensive and multidimensional set of primary neurocognitive outcomes. Through expert consensus among the study group, we identified seven domains of neurocognition that would be most representative of TBI-related impairment consisting of: Episodic Memory, Attention, Processing Speed, Working Memory, Executive Functioning, Verbal Fluency, and Fine Motor and Dexterity. From the battery of traditional and NIHTB-CB tests, we parsimoniously selected specific subtests or indices scores for each domain. The components of each domain are listed in Table 1 and further detail on the test instruments and measures is provided below.

California Verbal Learning Test-II (CVLT-II): Verbal episodic memory was measured using the Trials 1–5 Total Recall score and Long Delay Free Recall score (Delis et al., 2000). For each of the five trials, participants hear a list of 16 words, in the same order, and then are asked to recall the words in any order after each trial (Total Recall), and then again after 30 minutes (Long Delay Free Recall). Test-retest reliability for the standard forms, which are the ones used in the current study, ranged from 0.80 (Total Trials 1–5 Recall) to 0.83 (Long-delay Free Recall), and there is also evidence of discriminability (Woods et al., 2006).

Brief Visuospatial Memory Test-Revised (BVMT-R): Visual episodic memory was assessed using the Trials 1–3 Total score and Delayed Recall score (R. Benedict, 1997). During each of the three 10-second learning trials, participants study a 2 X 3 array of six figures and are then asked to reproduce each figure in its correct location. After a 25-minute delay, participants are asked again to draw each figure in its correct location from memory. There is evidence of construct and criterion-related validity (R. H. B. Benedict et al., 1996). Reliability coefficients are high (0.96 to 0.97) for the three learning trials and for Delayed Recall (0.97). The test-retest reliability coefficients range from 0.60 (Trial 1) to 0.84 (Trial 3) (R. Benedict, 1997).

NIHTB-CB: The NIHTB-CB consists of multiple subtests that span most of the same neurocognitive domains as a traditional neuropsychological test battery (Weintraub et al., 2013). We prespecified the Picture Sequence test for episodic memory, Pattern Comparison

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for processing speed, List Sorting for working memory, and both the Dimensional Change Card Sort and Flanker Inhibitory Control for executive functioning.

NIH-TB-CB Picture Sequence test ––—Each picture in a thematic series is presented individually, centered on the screen, as an audio file describes its content. The picture is then moved to a fixed place on the screen. After all pictures are presented, the participant moves them into the originally presented sequence. Excellent test-retest reliability (0.77–0.84) has been reported, as well as evidence of convergent and discriminant validity (Dikmen et al., 2014).

NIH-TB-CB Pattern Comparison Processing Speed ––—Participants view two visual patterns and press a button to indicate whether they are the same or not the same. Good test-retest reliability (0.73–0.74) has been demonstrated, as well as evidence of convergent and discriminant validity (Carlozzi et al., 2014).

NIH-TB-CB List Sorting ––—This test was designed to assess working memory. It entails sorting and sequencing visually and auditorily presented stimuli. There is evidence of convergent and discriminant validity, as well as excellent test-retest reliability with an overall value of 0.77 (Tulsky et al., 2014).

NIH-TB-CB Dimensional change card sort test ––—This test is a measure of cognitive flexibility. Two target pictures are presented that vary along two dimensions (e.g., shape and color) and participants must match a series of pictures to the target pictures, first according to one dimension (e.g., color) and then according to the other dimension (e.g., shape). “Switch” trials are also employed, in which the participant must switch the dimension being matched. Excellent test-retest reliability (.81-.85) has been reported (Zelazo et al., 2014), as well as convergent and discriminant validity.

NIH-TB-CB Flanker Inhibitory control ––—In this task, participants are required to indicate the left–right orientation of a centrally presented stimulus while inhibiting attention to the potentially incongruent stimuli that surround it. On some trials, the orientation of the flanking stimuli is congruent with the orientation of the central stimulus, and on others it is incongruent. Performance on the incongruent trials provides a measure of inhibitory control. This task has excellent test-retest reliability (.83-.85) as well as the expected convergent and discriminant validity (Zelazo et al., 2014).

Trail Making Test (TMT): The TMT Part A was used to measure simple attention, and Part B was used to measure executive function (Reitan & Wolfson, 1994). Both parts of the TMT consist of 25 circles distributed across a sheet of paper. In Part A, the circles are numbered 1 – 25, and the participant is asked to draw lines to connect the numbers in ascending order. In Part B, the circles include both numbers and letters and the participant is asked to alternate between numbers and letters.

TMT Part B is known to be sensitive to a wide range of cognitive difficulties (Lamberty et al., 1994). Test-retest reliability is high for Trails A (0.83) and B (0.90) (DesRosiers & Kavanagh, 1987) in head injured patients. For intervals of 3 weeks to 1 year, test-retest

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reliability is moderate to high for Part A (r=0.36 to 0.79) and Part B (r=0.44 to 0.89) (Bornstein et al., 1987; Dikmen et al., 1999; Matarazzo et al., 1974). In terms of executive functioning, Part B is more associated with cognitive flexibility than set-shifting (Kortte et al., 2002).

Wechsler Adult Intelligence Scale 4th Edition (WAIS-IV): All subtests of the widely used WAIS-IV have demonstrated good psychometric properties (Wechsler, D. et al., 2008).

Processing speed was measured by the *WAIS-IV Processing Speed Index*, a composite of the timed tasks of Symbol Search and Coding (Wechsler, D. et al., 2008). During the Symbol Search task, the participant decides whether either of the two target symbols match any of the symbols in a search group. For the Coding task, the participant is presented with a series of boxes and must draw the symbol that corresponds to the number in each box based on a coding legend presented at the top of the page.

Working memory was measured with the *WAIS-IV Working Memory Index*, a composite of the Digit Span and Letter-Number Sequencing tasks (Wechsler, D. et al., 2008). The Digit Span test consists of the examiner reading lists of numbers, and, based on instruction, the participant repeats the number sequence in the same order, backwards, or in ascending order. For Letter-Number Sequencing, the examiner reads a list of numbers and letters, and the participant recalls the list of numbers in ascending order and the letters in alphabetical order.

The *WAIS-IV Visual Puzzles* task was used to measure executive functioning / nonverbal reasoning. The participant views a puzzle and selects three options that, when combined, reconstruct the puzzle (Wechsler, D. et al., 2008).

Delis–Kaplan Executive Function System Verbal Fluency Test: Verbal fluency was evaluated using the Letter Fluency and Category Fluency tasks (Delis et al., 2001), which assess the ability to generate words quickly according to specified rules. Per the manual, this subtest has adequate psychometric properties including internal consistency and stability. Both types of fluency have been found to be sensitive to mild TBI (Raskin & Rearick, 1996). A meta-analysis found that category fluency was more sensitive to lesions of the temporal lobes, while both letter and category fluency was associated with frontal lesions (Henry & Crawford, 2004).

Grooved Pegboard: This widely used timed task was used to measure fine motor and dexterity skills linked to neurocognition (Klove, 1963). It has been found as a reliable source for testing manual dexterity. Retest reliability of this assessment is adequate (.72-.74) (Yancosek & Howell, 2009). Moderate/high associations have been reported with measures of attention (Schear & Sato, 1989; Strenge et al., 2002) and perceptual speed (Schear & Sato, 1989). Weak/modest associations have been noted between pegboard scores and daily functioning after head injury (Farmer & Eakman, 1995).

Performance Validity:

A review of performance validity testing and expert consensus panel in neuropsychology both recommend stand-alone and embedded performance validity indicators for cognitive

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testing (Lippa, 2018; Sweet et al., 2021). In the current study, performance validity was assessed by one stand-alone instrument, the *Medical Symptom Validity Test (MSVT)*, applying the developer recommended cut-off scores (Green et al., 2011) and two embedded measures, the *Reliable Digit Span* from the *WAIS-IV* (Schroeder et al., 2012) and the *Forced Choice Recognition* trial from the *CVLT-II* (Woods et al., 2006). These measures of performance validity have been tested previously among an OEF/OIF/OND Veteran population with mild TBI (Clark et al., 2014). Participants were excluded from analyses if they scored below recommended cut-offs on any one of these three performance validity tests (PVTs).

Medications:

Lists of current medications were collected at the time of cognitive performance testing and categorized into pharmacologic classes. For the purposes of the current analyses, we grouped relevant medication classes into one of the following three major categories: antidepressant, cognitive-enhancing (Stimulant, Cholinesterase Inhibitor, NMDA Receptor Antagonist), and or potential cognitive impairing (Antipsychotic, Alpha Adrenergic Agonist, Anti-Epileptic Agent, Anticholinergic, Antihistamine, Barbiturate, Benzodiazepine, Beta-Adrenergic Blocker, Cannabinoid, Central Alpha 2 Adrenergic Agonist, Nonbenzodiazepine Anxiolytic, Nonbenzodiazepine Hypnotic, Opioid Agonist, and central acting Muscle Relaxant).

Candidate covariates

Based on our literature review and expert consensus among the author group, selected demographics and measures were included as candidate covariates that we hypothesized could potentially contribute to cognitive performance. These covariates also included population-specific variables of interest such as military status and branch.

Demographics: Standardized demographic data was collected at baseline as queried in the Centers for Disease Control and Prevention-developed Behavioral Risk Factor Surveillance System (BRFSS) (Rolle-Lake & Robbins, 2020) and supplemented with military-specific information. We selected age, gender, race, ethnicity, education level, and marital status into the candidate covariates.

General intellectual functioning: The NIHTB-CB Picture Vocabulary task score was used to estimate pre-exposure intellectual function. This task assesses auditory comprehension of single words with different levels of difficulty and measured with an auditory word-picture matching paradigm (Gershon et al., 2014). Excellent test-retest reliability (0.80) has been demonstrated, as well as evidence of convergent and discriminant validity.

Military Occupational: Military status (current versus former), military service branch, total number of months on combat deployments, and combat intensity via section D of the Deployment Risk and Resiliency Inventory, Version 2 (DRRI-2) (Vogt et al., 2013). Additionally, during the lifetime TBI interview process, we queried the total number of controlled military-related blast exposures and for analyses classified as none, low (1–9),

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medium (10–89), or heavy (>89) because of heavily bimodal distribution at the floor and ceiling (99 or more).

Psychosocial: The following were evaluated as covariates: PTSD status via the PTSD Checklist for the Diagnostic and Statistical Manual, 5th edition (PCL-5) with total score > 33 indicating clinically significant PTSD symptoms (Blevins et al., 2015); depression via the Patient Health Questionnaire-9, a widely used 9-item rating of current (prior two-week) depression symptoms with total scores ranging from 0 (None) to 27 (Severe) (Kroenke et al., 2001); illicit drug use via the Drug Abuse Screening Test 10 questionnaire (Yudko et al., 2007); alcohol consumption within last three months via the Alcohol Use Disorders Test Consumption questionnaire categorized as none, non-hazardous use, or hazardous use (Kuitunen-Paul & Roerecke, 2018); social support via section O of the DRRI-2.

Other Comorbidities: Subjective sleep quality via the Pittsburgh Sleep Quality Index (Buysse et al., 1989); sleep apnea risk via the STOP-BANG questionnaire with high risk classified as STOP-BANG ≥ 3 (Chung et al., 2016); pain-related dysfunction via the TBI Quality of Life Pain Inhibition short form (Lange et al., 2016); neurobehavioral somatic symptoms using the Somatosensory (range: 0 to 28) and Vestibular (range: 0–12) sub-scales of the Neurobehavioral Symptom Inventory, where higher scores indicate higher severity (Meterko et al., 2012); self-reported history of Attention Deficit (Hyperactivity) Disorder (AD[H]D); and measured body mass index (BMI) were entered as relevant covariates.

Statistical methods:

To derive the final Z-scores for the seven cognitive domains of interest, Z-scores within the study sample were first calculated for all component neurocognitive tests using raw component test scores, their sample mean, and sample standard deviation. Subjects were included if at least one of the seven scores was non-missing. These component Z-scores were then averaged for each subject (i.e., sum of non-missing component Z-scores divided by number of non-missing component scores), following the definition of the domain, to generate the domain score of the subject. Pearson's correlation coefficients were calculated pairwise between the seven domains to preliminarily assess their interrelationship.

Univariable linear regression models assessed differences in each of the cognitive domain outcomes across the three main mTBI groups of interest (non-mTBI control as the reference versus 1–2 and 3+ lifetime mTBIs). Similarly, we also ran seven sets of univariable regression models for each of the candidate covariates, which confirmed significant relationships for every selected covariate on at least one cognitive domain (results not shown). Given this, and rather than selecting a separate set of covariates for each cognitive domain outcome, we used the entire set of candidate covariates described earlier as a uniform adjustment in the multivariable models.

Multivariable linear regression was the primary approach for examining the conditional relationship between mTBI groups and each of the seven neurocognitive domain outcomes separately while adjusting for the covariates. Regression coefficients and 95% confidence intervals (CIs) were reported. The coefficient with leading "10×" means the interpretation of the coefficient is based on an increment of 10 times the original unit of the variable.

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In addition to the primary analysis focusing on the three mTBI groups, we also performed a sensitivity analysis replacing the three mTBI groups with the number of mTBIs as a continuous variable, and also with total number of blast-related mTBIs. A subset analysis was conducted among participants with mTBI history to study time since first and last mTBI events. We also compared medication use across TBI groups using chi-squared or Kruskal-Wallis test for categorical or skew continuous variable, respectively.

As we analyzed seven cognitive outcomes, we used Holm's adjustment for multiple comparisons to adjust the p-values (Holm, 1979). The Holm's method compares each p-value to a threshold of 0.05/(7-k), where k is the rank of the raw p-value among the 7 raw p-values. Since it is difficult to implement different significance thresholds across multiple predictors and outcomes, we instead reported "adjusted p-values" by multiplying each raw p-value by (7-k) to enable uniform comparisons with the single conventional 0.05 significance threshold. We reported both sets of p-values, raw ("p-values") and after Holm's adjustment ("adjusted p-values"). We focused on comparing adjusted p-values with 0.05 to determine statistical significance. Note that the 95% CIs reported with each coefficient were not adjusted for multiple comparisons.

We used the generalized variance inflation factor (GVIF) to assess multicollinearity among covariates in our multivariable model settings. Multicollinearity was considered tolerable if the GVIF was <2.4, which is equivalent to a conventional VIF<5 (Gareth James, Daniela Witten, Trevor Hastie, and Robert Tibshirani, 2014). All statistical analyses were implemented using R v. 4.0.3.(R: A Language and Environment for Statistical Computing., n.d.)

Transparency and Openness (TOP)

The study and its investigators adhered to the highest level of TOP guidelines in conducting and reporting this study.

Availability of data and material:

Data used in this study are available to the public through the Federal Interagency Brain Injury Research (FITBIR) Informatics System.

RESULTS

Participants:

The available sample included 1,551particiapants and of those, 241 failed at least one of the three PVTs and were excluded, resulting in a final analysis sample size of 1,310. Further exclusions based on missing data varied by outcome domain and are depicted in the consort diagram (Figure 1). Table 2 shows the demographic and clinical characteristics of the entire sample and each of the main mTBI groups of interest: TBI negative controls (no TBIs, n=256), non-repetitive mTBI (1–2 lifetime mTBIs; n=614), and repetitive mTBI (3+ mTBIs; n=440). Overall, the sample's mean age at enrollment was 39.7 years and their mean time since index event was 9.7 years. Across TBI groups, time from index event ranged from 8.9 years for repetitive mTBI to 10.2 for controls. Time since index event for each TBI

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group is also presented graphically as box plots in Figure 2. Overall, the sample was diverse racially (27% non-White) and ethnically (17% Hispanic), was predominantly male (87%), educated with at least some college or technical school (86%), had an enlisted rank (84%), and served in the Army (65%). Regarding medications, there were no differences across TBI groups for being on an antidepressant (p=0.24) or a cognitive-enhancing medication (p=0.28). The repetitive mTBI group was receiving more medication classes that might compromise cognition (p=0.003), but the mean difference (0.2) and effect size (Cohen's d=0.18) versus the TBI negative controls were very small.

Cognitive performance across mTBI groups and their unadjusted comparisons

The mean Z-scores for the seven cognitive performance measures are shown in the top portion of Table 3 stratified by mTBI group (0, 1–2, 3+ lifetime mTBIs). The strength of correlation between the seven cognitive domains within our sample was generally in the 'moderate' range (Cohen, 1988), with values ranging from r=0.19 to r=0.49 (full results are available online in Supplemental Table S1). The bottom portion of Table 3 displays the results of the univariate regression models that compare the mTBI positive groups to the TBI negative controls. Neither mTBI positive group (repetitive, non-repetitive) was significantly different from the TBI negative control group for any of the respective cognitive domain Z-scores after applying the Holm's correction for the seven comparisons (all adjusted p-values > 0.05). Coefficients for the comparison of 1–2 mTBIs to no TBIs ranged from −0.09 (Episodic Memory and Processing Speed) to 0.02 (Verbal Fluency). Coefficients for the comparison of 3+ mTBIs to no TBIs ranged from −0.17 (Fine Motor and Dexterity) to 0.18 (Verbal Fluency). For the non-repetitive TBI group (1–2 mTBIs) versus controls, adjusted p-values ranged from p=0.09 (Executive Function) to 1 (two domains). For repetitive mTBI (3+ mTBIs) versus controls, p-values ranged from p=0.06 (Verbal Fluency) to 1 (three domains).

Multivariable regression analyses for groups with 1–2 and 3+ lifetime mTBIs versus TBI negative

Table 4 displays the results of the multivariable regression analyses that compare the cognitive performance between the two TBI positive groups and the TBI negative controls while adjusting for covariates. Because of the use of seven cognitive domains for the primary outcome, Table 4 is divided into 4A and 4B. The top rows in both 4A and 4B show the findings for the regression coefficients and significance testing comparing mTBI groups, which is the independent variable of interest. Below that, the remainder of the rows in the table report coefficients and significant testing findings for the covariates.

Neither of the mTBI positive groups, 1–2 lifetime mTBIs (non-repetitive) or 3+ lifetime mTBIs (repetitive), were significantly different from the mTBI negative control group on any cognitive outcome after adjusting for covariates and multiple comparisons. Coefficients for the comparison of 1–2 mTBIs to no TBIs ranged from −0.09 (Attention) to 0.05 (Verbal Fluency) and all adjusted p-values were 1 except for Executive Function (p=0.42). Coefficients for the comparison of 3+ mTBIs to no TBIs ranged from −0.04 (Processing Speed and Executive Function) to 0.17 (Verbal Fluency) and the only adjusted p-value under 1 was Verbal Fluency (adjusted p=0.15). There was no presence of multicollinearity in any

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model (all GVIF < 2.4, full results available on-line in supplementary Table S2). Covariates with significant findings after adjusting for multiple comparisons (adjusted $p<0.05$) were age, sex, race, education, estimated pre-exposure intellectual function, controlled blast, and vestibular symptoms. Age and estimated intellect were consistently related across all outcomes (adjusted p=0.01). Females performed better than males on three domains: episodic memory, processing speed, and fine motor and dexterity.

Sensitivity analyses for continuous number of mTBIs, number of blast-related mTBIs, and time since first and last mTBI.

The multivariable models described above were repeated in sensitivity analyses replacing the 3 group mTBI categorical variable with the number of mTBIs as a continuous variable (Table S3) and separately by total number of blast-related mTBIs (Table S4). We also conducted a sensitivity analysis repeating the above multivariable regression models within the mTBI subgroup, comparing 1–2 mTBIs versus 3+ mTBIs and also controlling for time since first and time since last mTBI as additional covariates (Table S6A and S6B). Similar to the primary analysis, none of these sensitivity analyses showed significant relationships of mTBIs with any of the seven cognitive domain outcomes after adjustment for multiple comparisons, with all of the adjusted p-value for mTBIs above 0.05 even before adjustment except for total number of blast-related mTBIs on Verbal Fluency (raw p=0.028; adjusted p=0.2) and repetitive versus non-repetitive mTBI on Verbal Fluency (raw p=0.015; adjusted p=0.1). For all of these additional models, all GVIF values were below 2.4, indicating no evidence of multicollinearity (Table S5).

DISCUSSION

This study examined whether remote mTBI(s) were associated with lower cognitive functioning relative to a negative mTBI history. Using cross-sectional analyses of a large, well-characterized sample of combat-exposed Veterans and SMs and objective neuropsychological measures, we found no differences in group cognitive performance for either those with non-repetitive (1–2 lifetime) or repetitive (3+ lifetime) mTBIs versus TBI negative controls. Additional sensitivity analyses also showed non-significance for all other TBI explanators examined, namely number of mTBIs as a continuous variable, number of blast-related mTBIs, and years since first and last mTBI. These findings align with prior studies and provide some of the strongest evidence to date that in unselected mTBI cases, lower cognitive performance does not chronically persist relative to controls (Belanger et al., 2005; Binder et al., 1997; Frencham et al., 2005; Karr et al., 2014; Rohling et al., 2011; Schretlen & Shapiro, 2003). Although not part of our primary analyses, our negative findings for blast-related mTBI also provide strong evidence against blast-related mTBI having a unique deleterious chronic effect on cognition. Clinically, our findings demonstrate that the average Veteran or SM who experiences one or more mTBIs should not expect to have chronically lingering challenges with cognitive ability due to mTBI alone.

Of all the covariates examined in our models, only age and estimated pre-exposure intellectual function were consistently associated with statistically significant differences across all seven cognitive domains (all adjusted p=0.01). The strong association with lower

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scores as age increased was expected given our use of raw scores rather than population-normed scores to calculate the sample-based Z-scores. As also expected, higher estimated pre-exposure intellectual function (NIHTB-CB Picture Vocabulary test) was related to higher scores on other cognitive measures, and education level had a significant effect on four domains. Additionally, females scored better than males on measures of episodic memory, processing speed, and fine motor skills. These sex-related findings are consistent with the literature in the general population, especially for episodic memory (Asperholm et al., 2019) and processing speed (Camarata & Woodcock, 2006).

While providing an encouraging message to Veterans, SMs, and providers, these negative findings do not rule out the potential for a vulnerable subset of individuals who do experience chronic objective cognitive changes after mTBI. Future study is recommended to assess rates of cognitive impairment using thresholds of cognitive performance as a function of TBI group membership while adjusting for other factors. If present, that might be better elucidated with a within-subjects, before-after, longitudinal study design. Additionally, our cross-sectional design did not directly address the question of greater cognitive decline over time from neurodegeneration or other delayed mTBI manifestation. We plan to test both of these hypotheses in future LIMBIC-CENC PLS analyses as we continue to reassess the cohort longitudinally and examine any within-subjects changes over time, including those who may sustain a new mTBI.

The physical and mental health symptom measure covariates showed less significance in the models than anticipated, but results were consistent with smaller studies that also measured performance validity (Wisdom et al., 2014). A separate, concurrent LIMBIC-CENC analysis is focusing more specifically on the interaction between PTSD and cognitive performance and may yield discrete findings. Vestibular symptoms on the NSI had a significant effect on fine motor scores, with higher self-reported symptom levels associated with poorer performance. This finding raises the question of how much this task (i.e., completion times on the Grooved Pegboard test) relates to neurocognition versus vestibular or motor control problems of any etiology. The lack of stronger evidence for significance of other symptom measures such as pain, sleep, and depression may in part be explained by our exclusion of PVT failures. Model overfitting may be another explanation (see further below).

The current study's findings should be considered together with the literature at large to best judge clinical implications. In comparison to TBI negative controls, individuals with remote mTBI history, especially those with repetitive mTBI, are well-documented to have greater *self-reported* cognitive difficulties (Walker, Hirsch, et al., 2018). Our new findings add to mounting evidence that most individuals with remote mTBI(s) do not have objective cognitive deficits that might explain their self-reported cognitive difficulties (Soble et al., 2013). This highlights the importance of a holistic treatment approach to include stress management techniques and treatment of other commonly comorbid conditions associated with cognitive symptoms such as PTSD, pain, insomnia, and depression. Providers should acknowledge, address and show empathy for patients' postconcussive experiences. However, it is important that providers do not suggest to their patients that mTBI results in long term, severe cognitive deficits; in some cases, it is possible that a focus on the TBI diagnosis may be unhelpful or even counter-productive (e.g., if fear of mTBI-related cognitive deficits

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prevents engagement in safe and healthy activities, or discourages other evidence-based treatment for comorbidities such as PTSD). For patients endorsing persisting problems with cognitive functioning, cognitive rehabilitation is still considered the standard of care, but it is crucial to focus on compensatory strategies and other behavioral training rather than on improving objective cognitive functioning deficits which are not as likely as self-reported cognitive symptoms (i.e., perceived cognitive deficits) (Cooper et al., 2017). Psychotherapy also seems well-suited to address stress-related symptoms and provide reinforcement for use of cognitive compensatory strategies (Cooper et al., 2015). Notwithstanding the lower than expected association of symptom measures to objective cognitive performance in the current study, addressing modifiable conditions such as depression/anxiety, PTSD, insomnia/sleep disorders, and pain would likely have indirect benefit, if not direct, on subjective cognitive symptoms and possibly objective cognitive performance as well.

The clinical implications of this study's findings have heightened importance because of the ubiquity of stories on concussion in the news and popular press indicating concussions likely will lead to a deteriorating course of cognitive and behavioral difficulties, which has created unique challenges for healthcare providers, particularly neuropsychologists who perform cognitive evaluations, in their efforts to treat those with a history of concussion(s) (Ahmed & Hall, 2017; Baugh et al., 2017, 2021). As has been empirically demonstrated, beliefs, attributions and expectations may adversely impact recovery from concussion (Ozen & Fernandes, 2011). As a provider, it is extremely difficult to counter the effects of the media with empirically-balanced information, such as that found in this study and many others. This is thought to occur because people associate concussion with negative outcomes and therefore experience a type of "diagnosis threat" (Suhr & Gunstad, 2002). From a clinical perspective, it is important to note that attributional styles are mutable and can be successfully addressed (Peters et al., 2011) . However, the traditional model of neuropsychological assessment and subsequent feedback, which may provide reassurance in other clinical populations, often is ineffective in individuals with tightly held beliefs/attributions about concussion. Cross-disciplinary, behavioral approaches that draw upon elements of treatment for other chronic conditions might best serve any patients who may have negative beliefs and sequalae from concussion(s). For example, Belanger et al. (Belanger et al., 2020) advocate for a three-phased approach including: assessment and education, targeted interventions directed at specific symptoms and comorbidities, and psychotherapy to address any mental health issues. Future research is needed to test such approaches in longitudinal studies.

Future research should also consider repetitive low-level exposures as it relates to cognition. If there is cumulative brain damage from repetitive, sub-concussive, low-level blast exposures as evidence from other evaluation techniques suggests (Belding et al., 2021; Goldstein et al., 2012; Stone et al., 2020; Tate et al., 2013), it was not apparent on our cognitive testing. Using our original one-item measure, the only significant reduction was for verbal fluency in those with a medium level (10–89) of controlled blast exposures compared to none, but it was not significant for the high level (90+) group. The LIMBIC-CENC PLS has added a questionnaire on athletic head impact exposures and a consensus-developed questionnaire for cumulative military blast exposures for which information is

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still being collected on enrolled participants. Future research incorporating these instruments may provide additional insights.

Key strengths of this study include the very large and ethnically and racially diverse sample, the inclusion of mTBI-negative but deployed controls, and the exclusion of cases with profiles of invalid testing. Our study has the largest sample size to date with comprehensive neurocognitive testing in Veterans and SMs with blast-related mTBI. This is important because extant literature has demonstrated inconsistent findings on the enduring deleterious effects of blast-related mTBI versus blunt mTBI including on cognition (Belanger et al., 2009; Martindale et al., 2020). The use of dissimilar controls and/or inclusion of cases with diminished or feigned effort are both important sources of potential bias toward positive associations between mTBI and cognitive decline. Notably, our mTBI negative controls were recruited through the same processes as the mTBI positive participants which provided a relevant control group with similar background characteristics and experiences. For assuring valid performance effort, we utilized an aggressive approach by excluding any failures of either a gold-standard stand-alone test or either of two additional well-accepted embedded measures. Another strength was the *a-priori* designation of seven cognitive domain composite scores for the dependent variable and appropriately adjusting for Type 1 error. Due to the contrasting constructs of various neurocognitive processes, single composite scores have pitfalls for both validity and sensitivity. On the other hand, single cognitive test scores are prone to reliability concerns and comparing an excessive number of cognitive test scores increases risk of Type 1 error. The large sample size also permitted us to analyze and statistically adjust for the many covariates that might influence the relationship between remote mTBI history and cognitive performance. Finally, the use of measures recommended as NIH NINDS TBI common data elements allows other studies to compare their results to ours (Hicks et al., 2013; Report Viewer | NINDS Common Data Elements, n.d.)

There are some limitations to this study. Foremost is the cross-sectional design, which precludes understanding of later cognitive changes which may be due to TBI or other comorbidities as well as subtle changes that may be related to other aspects of deployment. The lack of difference in cognitive performance may be, in part, related to benefit gained from treatment since our participants had access to specialized brain injury rehabilitation services in the Military and/or Veterans healthcare system. Additionally, although we used a validated structured interview method with layers of quality assurance, the retrospective identification of historical mTBI is prone to recall bias. Although our use of pre-selected cognitive domain composite scores sharpened our scientific rigor, it is possible we may have not selected the most sensitive measures to capture cognitive effects. The relationships between the seven domains in our sample showed ‘moderate’ correlations, suggesting that further collapsing of domains may be possible. While our consideration of multiple potential confounders is a strength, regression models are increasingly prone to overfitting as the number of covariates increases (Babyak, 2004). It seems unlikely that overfitting contributed to our null findings given that there were also no significant differences in preliminary univariable analyses comparing mTBI groups on the cognitive outcomes. We also did not implement any automated covariate selection methods in constructing our multivariable models.

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Constraints on Generalizability:

Given the LIMBIC-CENC research mission, our study sample consists entirely of current and former military SMs who often sustained mTBI during combat deployment and/or blast-related mTBI, so the findings may not generalize well to civilians. Because most of our recruitment/enrollment sites are based at VA medical facilities, these findings may not generalize to sizeable population of former SMs who receive medical care entirely at non-VA medical centers. Our study sample, which mirrored the broader U.S. military population in gender make up, was predominantly male, so our findings may also not generalize well to women.

Conclusion:

This study found no evidence that remote mTBI(s) influence objective cognitive performance among SMs and Veterans with combat exposure history who passed performance validity measures. This suggests that self-reported concerns about cognitive difficulties in persons in the chronic phase following mTBI are likely best treated with a holistic approach that considers common comorbid conditions and situational factors that could be associated with longstanding cognitive complaints. Strategies for addressing misattribution may also be beneficial and further research on behavioral interventions for patients with tightly held negative beliefs on the impact of their remote concussions is also recommended. Given the limitations of our cross-sectional design and between-subjects comparison, future study with the LIMBIC-CENC PLS cohort will be performed using longitudinal design to assess within-subjects changes and before-after data for participants with incipient mTBI as well as assessing rates of cognitive impairment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key Points:

Question:

Is cognitive performance altered long-term after mild traumatic brain injury (mTBI) relative to non-TBI controls?

Findings:

Among combat-exposed Veterans and Service Members (SMs), neither of the mTBI positive groups, non-repetitive (1–2) or repetitive (≥3), differed from the TBI negative controls on any cognitive testing domain when adjusting for other factors.

Importance:

Remote mTBI alone, even if repetitive, does not cause objective cognitive problems in the average Veteran or SM. A holistic healthcare approach including comorbidity assessment is indicated for patients reporting chronic cognitive difficulties after mTBI(s), and strategies for addressing misattribution may be beneficial.

Next steps:

Future study is recommended with longitudinal designs to assess any potential within-subjects decline from possible neurodegeneration.

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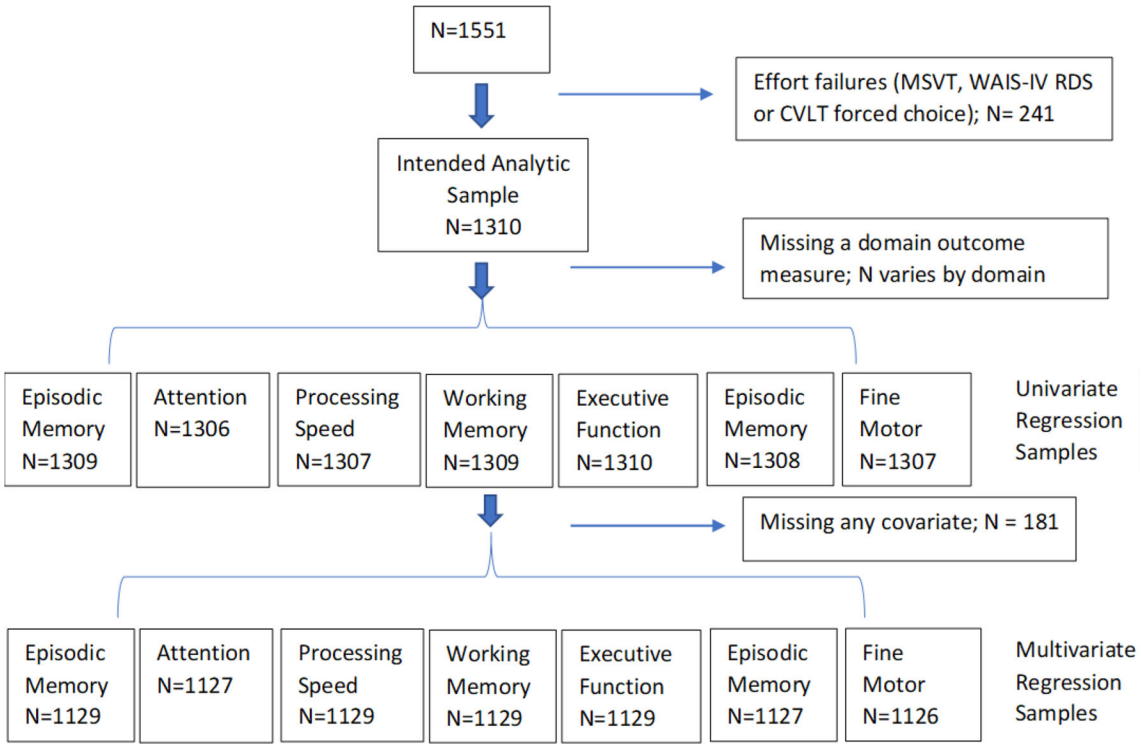

Figure 1.

Consort Diagram

Abbreviations: MSVT= Medical Symptom Validity Test; WAIS-IV= Wechsler Adult Intelligence Scale 4th Edition; RDS= Reliable Digit Span CVLT-II = California Verbal Learning Test-II

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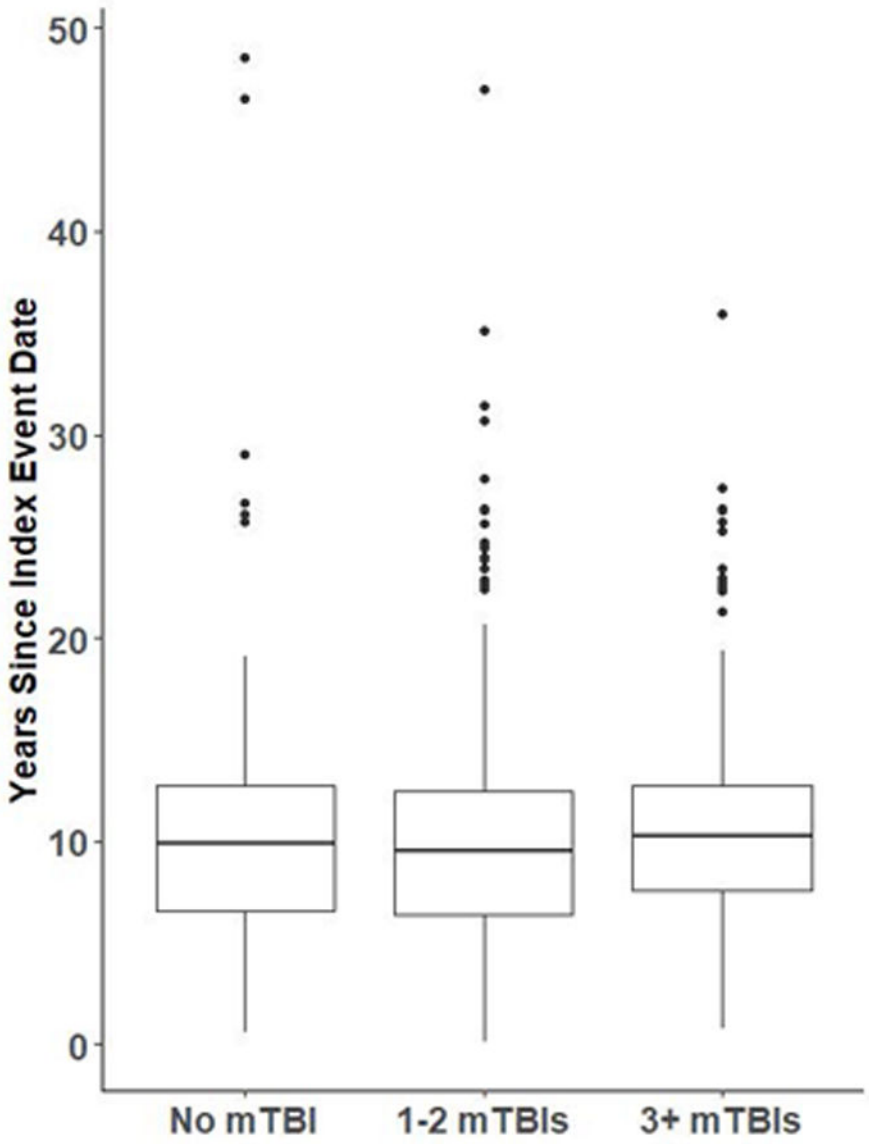

Figure 2.
Years Since Index Event Abbreviation: mTBI = mild traumatic brain injury.

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Table 1.

Pre-specified Neurocognitive Outcomes

Domains	Component Test Scores
Episodic memory	CVLT-II: Trials 1–5 total; Long Delay Free Recall BVMT-R: Total Recall NIH-TB-CB Picture Sequence
Attention	TMT Part A
Processing speed	WAIS-IV Processing Speed Index NIH-TB-CB Pattern Comparison
Working Memory	WAIS-IV Working Memory Index NIH-TB-CB List Sorting
Executive functioning	TMT Part B WAIS-IV Visual Puzzles NIH-TB-CB Dimensional change card sort test NIH-TB-CB Flanker Inhibitory control
Verbal Fluency	D-KEFS VFT: Letter fluency; Category fluency
Fine Motor & Dexterity	Grooved Pegboard: Dominant; Non-dominant

Abbreviations: CVLT-II = California Verbal Learning Test-II; BVMT-R = Brief Visuospatial Memory Test-Revised; NIH TB-CB = NIH Toolbox Cognition Battery; TMT = Trail Making Test; WAIS-IV = Wechsler Adult Intelligence Scale 4th Edition; DKEFS = the Delis–Kaplan Executive Function System

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Table 2.

Characteristics of Sample and mTBI groups.

Variable	Type/Level	Total N=1310	No mTBI: N=256	1–2 mTBIs: N=614	3+ mTBIs: N=440	Missing
Age	[mean (SD)] Years	39.7 (9.7)	39.6 (10.2)	39.3 (10.0)	40.3 (8.9)	0
Index Event Date	[mean (SD)] Years since	9.9 (4.9)	10.1 (5.4)	9.7 (5.0)	10.3 (4.4)	0
Gender	Female	169 (13%)	58 (23%)	78 (13%)	33 (8%)	0
	Male	1141 (87%)	198 (77%)	536 (87%)	407 (92%)	
Race	American Indian or Alaska Native	8 (1%)	2 (1%)	2 (0%)	4 (1%)	0
	Asian	22 (2%)	9 (4%)	6 (1%)	7 (2%)	
	Black or African American	242 (18%)	61 (24%)	127 (21%)	54 (12%)	
	Pacific Islander	10 (1%)	2 (1%)	3 (0%)	5 (1%)	
	White	953 (73%)	175 (68%)	437 (71%)	341 (78%)	
	Other	59 (5%)	4 (2%)	31 (5%)	24 (5%)	
	Don’t know/Not sure/Refused	16 (1%)	3 (1%)	8 (1%)	5 (1%)	
Ethnicity	Hispanic or Latino	229 (17%)	49 (19%)	115 (19%)	65 (15%)	0
	Not Hispanic or Latino	1066 (81%)	205 (80%)	495 (81%)	366 (83%)	
	Don’t know/Not sure/Refused	15 (1%)	2 (1%)	4 (1%)	9 (2%)	
Race/Ethnicity Dichotomized	White or Asian Non-Hispanic	801 (62%)	146 (57%)	359 (59%)	296 (69%)	21
	All others (e.g. Black, Hispanic)	488 (38%)	108 (43%)	247 (41%)	133 (31%)	
Married	Divorced/Separated/Widowed	315 (24%)	64 (25%)	160 (26%)	91 (21%)	1
	Married/Couple	768 (59%)	143 (56%)	344 (56%)	281 (64%)	
	Never married	226 (17%)	49 (19%)	110 (18%)	67 (15%)	
Education	Any High school, no college	184 (14%)	37 (14%)	102 (17%)	45 (10%)	0
	Some college or technical school	533 (41%)	98 (38%)	246 (40%)	189 (43%)	
	College (4+ years) graduate	593 (45%)	121 (47%)	266 (43%)	206 (47%)	
BMI	[mean (SD)]	29.9 (5.1)	29.7 (5.5)	30.0 (5.1)	29.9 (5.0)	11
AD(H)D history	No	1200 (92%)	240 (94%)	565 (92%)	395 (90%)	6
	Yes	104 (8%)	14 (6%)	47 (8%)	43 (10%)	
Military Rank	Enlisted	1099 (84%)	213 (84%)	529 (86%)	357 (81%)	4
	Officer	207 (16%)	42 (16%)	83 (14%)	82 (19%)	

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Variable	Type/Level	Total N=1310	No mTBI: N=256	1–2 mTBIs: N=614	3+ mTBIs: N=440	Missing
Service Branch	Army	856 (65%)	162 (63%)	402 (65%)	292 (66%)	0
	Marine Corps	192 (15%)	27 (11%)	97 (16%)	68 (15%)	
	all others	262 (20%)	67 (26%)	115 (19%)	80 (18%)	
Military Status	Veteran	1068 (82%)	220 (86%)	520 (85%)	328 (75%)	3
	Active/Reserve	239 (18%)	35 (14%)	93 (15%)	111 (25%)	
Deployed Time	[mean (SD)] Months	19.7 (13.2)	17.4 (11.2)	18.8 (12.6)	22.2 (14.7)	27
Combat Intensity	[mean (SD)] DRRI-2-D	37.7 (15.3)	30.2 (12.3)	37.9 (15.3)	41.9 (15.4)	4
Social Support	[mean (SD)] DRRI-2-S	38.6 (8.6)	39.6 (8.5)	38.5 (8.6)	38.1 (8.6)	0
Depression	[mean (SD)] PHQ-9	7.7 (5.9)	5.8 (5.5)	7.9 (6.1)	8.7 (5.8)	15
Pain	[mean (SD)] TBI-QoL Pain Intensity	21.7 (10.4)	17.5 (9.1)	21.9 (10.5)	24.0 (10.4)	69
Pre-exposure Intellectual Function Estimate	[mean (SD)] NIH-TB-CB Picture Vocabulary	108.5 (8.2)	107.4 (8.7)	107.7 (8.2)	110.3 (7.6)	54
PTSD symptoms	[mean (SD)] PCL-5	25.5 (18.9)	18.6 (17.0)	26.1 (19.4)	28.7 (18.3)	14
Alcohol use (Audit-C) (past three months)	User at Hazardous level	474 (36%)	79 (31%)	221 (36%)	174 (40%)	7
	User Non-hazardous level	603 (46%)	136 (53%)	269 (44%)	198 (45%)	
	Abstinent	226 (17%)	40 (16%)	120 (20%)	66 (15%)	
Drug Use (DAST-10) (past year)	None	1093 (84%)	217 (85%)	508 (83%)	368 (84%)	7
	Yes	210 (16%)	37 (15%)	103 (17%)	70 (16%)	
Sleep Quality	[mean (SD)] PSQI	9.8 (4.6)	8.2 (4.6)	9.7 (4.5)	10.7 (4.3)	32
Sleep Apnea (High Risk on STOP-BANG)	No	498 (39%)	130 (52%)	232 (39%)	136 (32%)	34
	Yes	778 (61%)	122 (48%)	366 (61%)	290 (68%)	
Controlled Blast Exposures	None (0)	497 (38%)	136 (53%)	231 (38%)	130 (30%)	0
	Low (1–9)	338 (26%)	52 (20%)	171 (28%)	115 (26%)	
	Medium (10–89)	320 (24%)	46 (18%)	144 (23%)	130 (30%)	
	Heavy (>89)	497 (38%)	136 (53%)	231 (38%)	130 (30%)	
Somatosensory Symptoms	[mean (SD)] NSI SS Domain	6.1 (4.7)	3.9 (4.0)	6.0 (4.6)	7.5 (4.8)	9
Vestibular Symptoms	[mean (SD)] NSI V Domain	2.0 (2.1)	0.9 (1.4)	1.9 (2.1)	2.6 (2.3)	7

Abbreviations: ADHD = Attention Deficit Hyperactivity Disorder; AUDIT-C= Alcohol Use Disorders Test Consumption; DAST-10= Drug Abuse Screening Test- 10; DRRI-2= Deployment Risk and Resiliency Inventory, Version 2; NIH TB-CB = NIH Toolbox Cognition battery; NSI= Neurobehavioral Symptom Inventory; PCL-5= PTSD Checklist for the Diagnostic and Statistical Manual, 5th edition; PSQI= Pittsburgh Sleep Quality Index; PHQ-9=Patient Health Questionnaire-9; TBI QoL= Traumatic Brain Injury Quality of Life.

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Table 3.

Unadjusted Mean (SD) Z-scores for cognitive performance (top) with univariate linear regression models (bottom)

	No mTBI (N=256)	1–2 mTBIs (N=614)			3+ mTBIs (N=440)			Missing
Episodic Memory	0.06 (0.77)	-0.03 (0.78)			0.01 (0.76)			1
Attention	0.03 (0.99)	-0.05 (1.08)			0.05 (0.88)			4
Processing Speed	0.09 (0.83)	0.00 (0.81)			-0.06 (0.72)			3
Working Memory	-0.03 (0.74)	-0.02 (0.78)			0.04 (0.76)			1
Executive Functioning	0.06 (0.52)	-0.05 (0.63)			0.04 (0.64)			0
Verbal Fluency	-0.07 (0.86)	-0.05 (0.87)			0.11 (0.88)			2
Fine Motor & Dexterity	0.13 (0.86)	-0.02 (0.96)			-0.04 (0.93)			3
		Coefficient (95% CI)	**p-value**	**Adjusted p-value**	**Coefficient (95% CI)**	**p-value**	**Adjusted p-value**	**N**
Episodic Memory	-	-0.09 (-0.20,0.02)	0.12	0.60	-0.05 (-0.17,0.07)	0.44	1	1309
Attention	-	-0.08 (-0.22,0.07)	0.31	0.93	0.02 (-0.14,0.17)	0.83	1	1306
Processing Speed	-	-0.09 (-0.20, 0.03)	0.13	0.60	-0.15 (-0.27,-0.03)	0.015*	0.09	1307
Working Memory	-	0.01 (-0.10,0.12)	0.87	1	0.08 (-0.04,0.19)	0.20	0.80	1309
Executive Functioning	-	-0.11 (-0.20,-0.02)	0.013*	0.09	-0.02 (-0.12, 0.07)	0.65	1	1310
Verbal Fluency	-	0.02 (-0.11,0.15)	0.74	1	0.18 (0.05,0.32)	0.008*	0.06	1308
Fine Motor & Dexterity	-	-0.15 (-0.29,-0.02)	0.028*	0.17	-0.17 (-0.32,-0.03)	0.020*	0.10	1307

* p-value < 0.05

Note: Higher positive values indicate better performance
Interpretation examples:
For the Executive Functioning outcome, those with 1–2 mTBIs have lower scores compared to those who have none, although this difference was not statistically significant after adjusting for multiple comparisons (coefficient = −0.11, 95% CI: −0.20,−0.02, p-value=0.013).
The “10 ×” is interpreted as “10 units increase” in DRRI-2, instead of the conventional “every 1 unit increase”. For example, when outcome is Fine Motor Dexterity, for every 10 units increase in DRRI-2, the domain scores decreased 0.04 unit (coefficient = −0.04, 95% CI: −0.07,−0.01, p-value=0.015).

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Table 4A.

Multivariable linear regression models for Veterans and Service Members with repetitive and non-repetitive mTBI versus those with no TBI history

	Episodic Memory			Attention			Processing Speed			Working Memory		
Variable	**Coefficient (95% CI)**	**p-value**		**Coefficient (95% CI)**	**p-value**		**Coefficient (95% CI)**	**p-value**		**Coefficient (95% CI)**	**p-value**	
		Raw	**Adjust**		**Raw**	**Adjust**		**Raw**	**Adjust**		**Raw**	**Adjust**
mTBI Positive Groups versus TBI Negative Controls												
1–2 mTBIs	−0.06 (−0.17, 0.05)	0.26	1	−0.09 (−0.24, 0.07)	0.26	1	−0.01 (−0.12, 0.10)	0.90	1	0.02 (−0.08, 0.13)	0.70	1
3+ mTBIs	−0.03 (−0.16, 0.09)	0.60	1	0.04 (−0.14, 0.22)	0.65	1	−0.04 (−0.17, 0.09)	0.54	1	0.02 (−0.10, 0.14)	0.76	1
Covariates												
Age	−0.03 (−0.03,−0.02)	<0.001	**0.01**	−0.03 (−0.04, −0.02)	<0.001	**0.01**	−0.03 (−0.04,−0.03)	<0.001	**0.01**	−0.02 (−0.03,−0.02)	<0.001	**0.01**
Gender: Male	−0.29 (−0.42,−0.15)	<0.001	**0.01**	−0.11 (−0.30, 0.09)	0.29	0.75	−0.36 (−0.50,−0.22)	<0.001	**0.01**	0.10 (−0.03, 0.23)	0.14	0.56
Race/Ethnicity: Non-Hispanic White/Asian	0.07 (−0.02, 0.16)	0.15	0.52	0.17 (0.04, 0.30)	0.013	0.06	0.07 (−0.02, 0.17)	0.13	0.52	0.13 (0.04, 0.21)	0.006	**0.04**
Married:Married/ couple	0.07 (−0.03, 0.17)	0.14	0.84	0.01 (−0.13, 0.15)	0.91	1	0.09 (−0.02, 0.19)	0.10	0.7	0.05 (−0.05, 0.15)	0.31	1
Never married	0.04 (−0.09, 0.17)	0.60	1	−0.04 (−0.22, 0.14)	0.65	1	−0.04 (−0.17, 0.09)	0.55	1	0.03 (−0.10, 0.15)	0.68	1
Education: Some College	−0.04 (−0.17, 0.08)	0.52	0.69	0.11 (−0.07, 0.29)	0.23	0.69	0.10 (−0.02, 0.23)	0.11	0.55	0.24 (0.12, 0.36)	<0.001	**0.01**
College Graduate	−0.02 (−0.15, 0.11)	0.73	0.73	0.10 (−0.09, 0.28)	0.29	0.58	0.21 (0.08, 0.34)	0.002	**0.01**	0.21 (0.09, 0.34)	<0.001	**0.01**
BMI	0.00 (−0.01, 0.01)	0.46	1	0.00 (−0.01, 0.01)	0.76	1	0.00 (−0.01, 0.01)	0.44	1	0.00 (−0.01, 0.01)	0.98	1
AD(H)D: Yes	−0.16 (−0.32,−0.01)	0.038	0.27	0.05 (−0.16, 0.27)	0.63	1	−0.05 (−0.20, 0.10)	0.52	1	−0.05 (−0.19, 0.10)	0.53	1
Service Branch:Army	−0.02 (−0.13, 0.09)	0.73	1	−0.10 (−0.25, 0.06)	0.22	1	−0.03 (−0.14, 0.08)	0.62	1	−0.06 (−0.17, 0.04)	0.22	1
Marine Corps	−0.01 (−0.16, 0.13)	0.85	1	0.11 (−0.09, 0.32)	0.29	1	0.02 (−0.13, 0.16)	0.81	1	0.00 (−0.14, 0.14)	0.98	1
Current Military:Yes	0.10 (0.00, 0.21)	0.06	0.36	0.09 (−0.06, 0.25)	0.23	1	0.03 (−0.08, 0.13)	0.65	1	0.13 (0.03, 0.23)	0.015	0.1
Deployed Time (yr)	−0.01 (−0.05, 0.04)	0.76	1	−0.01 (−0.07, 0.04)	0.63	1	0.04 (−0.01, 0.08)	0.09	0.63	0.02 (−0.02, 0.06)	0.42	1

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	Episodic Memory			Attention			Processing Speed			Working Memory		
Combat Intensity (10 × DRRI-2-C)	0.00 (−0.03, 0.03)	0.99	1	0.04 (−0.01, 0.09)	0.10	0.7	0.01 (−0.02, 0.05)	0.50	1	−0.02 (−0.05, 0.01)	0.27	1
Depression (PHQ-9)	0.00 (−0.01, 0.01)	0.94	1	−0.01 (−0.02, 0.01)	0.42	1	0.00 (−0.01, 0.01)	0.94	1	0.00 (−0.01, 0.01)	0.86	1
Pain (TBI-QOL)	0.00 (0.00, 0.01)	0.26	1	0.00 (−0.01, 0.01)	0.51	1	0.00 (0.00, 0.01)	0.27	1	0.00 (−0.01, 0.00)	0.37	1
Estimate Intellect (NIHTB-CB pic vocab)	0.02 (0.02, 0.03)	<0.001	**0.01**	0.01 (0.00, 0.02)	0.007	**0.01**	0.01 (0.01, 0.02)	<0.001	**0.01**	0.03 (0.02, 0.03)	<0.001	**0.01**
PTSD (PCL-5)	0.00 (−0.01, 0.00)	0.033	0.2	0.00 (−0.01, 0.00)	0.11	0.44	0.00 (−0.01, 0.00)	0.22	0.63	0.00 (−0.01, 0.00)	0.041	0.21
Hazardous Alcohol Use (AUDIT-C): Yes, non-hazardous	−0.03 (−0.12, 0.06)	0.54	1	−0.01 (−0.14, 0.11)	0.83	1	−0.03 (−0.12, 0.06)	0.51	1	0.03 (−0.06, 0.12)	0.48	1
Not user	−0.10 (−0.22, 0.02)	0.09	0.54	0.00 (−0.17, 0.17)	0.97	1	−0.11 (−0.23, 0.01)	0.07	0.49	0.03 (−0.09, 0.14)	0.62	1
Sleep Problems (PSQI)	0.01 (−0.01, 0.02)	0.41	1	0.00 (−0.01, 0.02)	0.60	1	−0.01 (−0.02, 0.01)	0.39	1	0.01 (0.00, 0.02)	0.023	0.16
Sleep Apnea High Risk (STOP-BANG)	−0.08 (−0.19, 0.02)	0.12	0.84	0.06 (−0.09, 0.21)	0.43	1	−0.06 (−0.17, 0.04)	0.24	1	−0.04 (−0.14, 0.06)	0.43	1
Controlled Blast Exposure: Low (1–9)	−0.01 (−0.15, 0.14)	0.93	1	0.08 (−0.12, 0.28)	0.44	1	0.00 (−0.14, 0.15)	0.95	1	−0.04 (−0.18, 0.10)	0.61	1
Medium (10–89)	−0.03 (−0.17, 0.11)	0.67	1	−0.04 (−0.24, 0.16)	0.72	1	−0.03 (−0.17, 0.11)	0.68	1	−0.02 (−0.16, 0.11)	0.76	1
Heavy (>89)	−0.04 (−0.19, 0.10)	0.56	1	−0.03 (−0.23, 0.17)	0.76	1	0.03 (−0.12, 0.17)	0.73	1	−0.09 (−0.22, 0.05)	0.23	1
Somatosensory Symptoms (NSI)	0.00 (−0.01, 0.02)	0.92	1	0.00 (−0.02, 0.02)	0.88	1	0.00 (−0.02, 0.01)	0.54	1	−0.01 (−0.02, 0.01)	0.36	1
Vestibular Symptoms (NSI)	−0.01 (−0.04, 0.02)	0.36	1	−0.01 (−0.05, 0.03)	0.54	1	−0.02 (−0.05, 0.01)	0.11	0.66	−0.01 (−0.04, 0.02)	0.55	1

Notes: Bolded covariates are significant after P < 0.05 corrected for multiple comparisons. Number of observations used to fit model, in order, are: 1129,1127,1129,1129

Abbreviations: ADHD = Attention Deficit Hyperactivity Disorder; AUDIT-C= Alcohol Use Disorders Test Consumption; DAST-10= Drug Abuse Screening Test- 10; DRRI-2= Deployment Risk and Resiliency Inventory, Version 2; NIH TB-CB = NIH Toolbox Cognition battery; NSI= Neurobehavioral Symptom Inventory PCL-5= PTSD Checklist for the Diagnostic and Statistical Manual, 5th edition; PSQI= Pittsburgh Sleep Quality Index; PHQ-9=Patient Health Questionnaire-9; TBI QoL= Traumatic Brain Injury Quality of Life.

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Table 4B.

Multivariable linear regression models for repetitive and non-repetitive mTBI versus TBI negative (continued)

	Executive Function			Verbal Fluency			Fine Motor & Dexterity		
variable	**Coefficient (95% CI)**	**p-value**		**Coefficient (95% CI)**	**p-value**		**Coefficient (95% CI)**	**p-value**	
		Raw	**Adjust**		**Raw**	**Adjust**		**Raw**	**Adjust**
mTBI Positive Groups versus TBI Negative Controls									
1–2 mTBIs	−0.08 (−0.16, 0.00)	0.06	0.42	0.05 (−0.08, 0.18)	0.42	1	−0.02 (−0.16, 0.12)	0.77	1
3+ mTBIs	−0.04 (−0.14, 0.05)	0.39	1	0.17 (0.03, 0.32)	0.022	0.15	0.01 (−0.15, 0.16)	0.95	1
Covariates									
Age	−0.02 (−0.02,−0.01)	<0.001	**0.01**	−0.01 (−0.02,−0.01)	<0.001	**0.01**	−0.03 (−0.04,−0.02)	<0.001	**0.01**
Gender: Male	−0.06 (−0.17, 0.04)	0.25	0.75	0.04 (−0.13, 0.20)	0.67	0.75	−0.27 (−0.44,−0.10)	0.002	**0.01**
Race/Ethnicity: Non−Hispanic White/Asian	0.15 (0.08, 0.22)	<0.001	**0.01**	0.00 (−0.11, 0.11)	0.94	0.94	0.05 (−0.07, 0.16)	0.41	0.82
Married: Married/couple	0.01 (−0.07, 0.09)	0.82	1	−0.05 (−0.17, 0.07)	0.38	1	−0.05 (−0.17, 0.08)	0.47	1
Never married	−0.05 (−0.15, 0.05)	0.34	1	0.01 (−0.14, 0.16)	0.90	1	−0.19 (−0.35,−0.03)	0.022	0.15
Education: Some College	0.07 (−0.03, 0.17)	0.16	0.64	0.07 (−0.08, 0.22)	0.34	0.69	0.21 (0.06, 0.37)	0.007	**0.04**
College Graduate	0.10 (0.00, 0.20)	0.06	0.18	0.22 (0.06, 0.37)	0.007	**0.03**	0.37 (0.21, 0.54)	<0.001	**0.01**
BMI	0.00 (−0.01, 0.00)	0.24	1	0.01 (0.00, 0.02)	0.06	0.36	−0.01 (−0.03, 0.00)	0.007	0.05
ADD: Yes	−0.10 (−0.22, 0.01)	0.09	0.54	−0.04 (−0.22, 0.14)	0.66	1	0.15 (−0.04, 0.34)	0.12	0.6
Service Branch:Army	−0.04 (−0.12, 0.04)	0.34	1	−0.08 (−0.21, 0.04)	0.20	1	−0.02 (−0.15, 0.11)	0.76	1
Marine Corps	−0.05 (−0.16, 0.06)	0.38	1	−0.09 (−0.27, 0.08)	0.28	1	−0.02 (−0.20, 0.16)	0.79	1
Current Military:Yes	0.01 (−0.07, 0.09)	0.82	1	0.06 (−0.07, 0.19)	0.37	1	0.00 (−0.14, 0.13)	0.97	1
Deployed Time (yr)	0.00 (−0.03, 0.03)	0.88	1	0.01 (−0.04, 0.06)	0.60	1	−0.01 (−0.06, 0.04)	0.74	1
Combat Intensity (10 × DRRI−2-C)	0.02 (−0.01, 0.04)	0.21	1	0.01 (−0.03, 0.05)	0.50	1	−0.02 (−0.06, 0.02)	0.31	1
Depression (PHQ9)	−0.01 (−0.02, 0.00)	0.16	1	0.00 (−0.02, 0.01)	0.95	1	0.00 (−0.02, 0.01)	0.72	1
Pain (TBIQOL)	0.00 (0.00, 0.01)	0.71	1	0.00 (−0.01, 0.01)	0.74	1	0.00 (0.00, 0.01)	0.22	1
Estimate Intellect (NIHTB-CB pic vocab)	0.02 (0.01, 0.02)	<0.001	**0.01**	0.03 (0.03, 0.04)	<0.001	**0.01**	0.01 (0.01, 0.02)	<0.001	**0.01**
PTSD (PCL5)	0.00 (−0.01, 0.00)	0.27	0.63	0.00 (−0.01, 0.00)	0.21	0.63	−0.01 (−0.01, 0.00)	0.026	0.18

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	Executive Function			Verbal Fluency			Fine Motor & Dexterity		
variable	**Coefficient (95% CI)**	**p-value**		**Coefficient (95% CI)**	**p-value**		**Coefficient (95% CI)**	**p-value**	
		Raw	**Adjust**		**Raw**	**Adjust**		**Raw**	**Adjust**
ETOH: Yes, non-hazardous	−0.05 (−0.12, 0.02)	0.18	1	0.00 (−0.11, 0.10)	0.95	1	0.01 (−0.10, 0.12)	0.85	1
Not user	−0.07 (−0.16, 0.02)	0.13	0.65	−0.03 (−0.17, 0.12)	0.73	1	−0.04 (−0.19, 0.11)	0.61	1
Sleep Problems (PSQI)	0.00 (−0.01, 0.01)	0.73	1	0.00 (−0.02, 0.01)	0.74	1	0.00 (−0.02, 0.01)	0.96	1
Sleep Apnea High Risk (STOP−BANG)	0.04 (−0.04, 0.12)	0.30	1	−0.04 (−0.16, 0.09)	0.57	1	−0.03 (−0.16, 0.10)	0.62	1
Controlled Blast Exposure: Low (1−9)	0.01 (−0.10, 0.12)	0.91	1	−0.12 (−0.29, 0.05)	0.17	1	−0.07 (−0.25, 0.11)	0.44	1
Medium (10–89)	0.00 (−0.11, 0.11)	0.96	1	−0.29 (−0.46,−0.12)	<0.001	**0.01**	0.03 (−0.14, 0.21)	0.70	1
Heavy (>89)	−0.02 (−0.12, 0.09)	0.79	1	−0.18 (−0.35,−0.01)	0.038	0.27	−0.12 (−0.29, 0.06)	0.20	1
Somatosensory Symptoms (NSI)	−0.01 (−0.02, 0.00)	0.07	0.49	0.00 (−0.02, 0.02)	0.96	1	0.00 (−0.02, 0.01)	0.65	1
Vestibular Symptoms (NSI)	0.00 (−0.02, 0.02)	0.88	1	−0.03 (−0.06, 0.01)	0.14	0.7	−0.05 (−0.09,−0.02)	0.003	**0.02**

Notes: Bolded covariates are significant after P < 0.05 corrected for multiple comparisons.

Number of observations used to fit model, in order, are: 1129,1127,1129,1129

Abbreviations: ADHD = Attention Deficit Hyperactivity Disorder; AUDIT-C= Alcohol Use Disorders Test Consumption; DAST-10= Drug Abuse Screening Test- 10; DRRI-2= Deployment Risk and Resiliency Inventory, Version 2; NIH TB-CB = NIH Toolbox Cognition battery; NSI= Neurobehavioral Symptom Inventory; PCL-5= PTSD Checklist for the Diagnostic and Statistical Manual, 5th edition; PSQI= Pittsburgh Sleep Quality Index; PHQ-9=Patient Health Questionnaire-9; TBI QoL= Traumatic Brain Injury Quality of Life;