Outcome Trends after US Military Concussive Traumatic Brain Injury

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Abstract

Care for US military personnel with combat-related concussive traumatic brain injury (TBI) has substantially changed in recent years, yet trends in clinical outcomes remain largely unknown. Our prospective longitudinal studies of US military personnel with concussive TBI from 2008–2013 at Landstuhl Regional Medical Center in Germany and two sites in Afghanistan provided an opportunity to assess for changes in outcomes over time and analyze correlates of overall disability. We enrolled 321 active-duty US military personnel who sustained concussive TBI in theater and 254 military controls. We prospectively assessed clinical outcomes 6–12 months later in 199 with concussive TBI and 148 controls. Global disability, neurobehavioral impairment, depression severity, and post-traumatic stress disorder (PTSD) severity were worse in concussive TBI groups in comparison with controls in all cohorts. Global disability primarily reflected a combination of work-related and nonwork-related disability. There was a modest but statistically significant trend toward less PTSD in later cohorts. Specifically, there was a decrease of 5.9 points of 136 possible on the Clinician Administered PTSD Scale (–4.3%) per year (95% confidence interval, 2.8–9.0 points, $p=0.0037$ linear regression, $p=0.03$ including covariates in generalized linear model). No other significant trends in outcomes were found. Global disability was more common in those with TBI, those evacuated from theater, and those with more severe depression and PTSD. Disability was not significantly related to neuropsychological performance, age, education, self-reported sleep deprivation, injury mechanism, or date of enrollment. Thus, across multiple cohorts of US military personnel with combat-related concussion, 6–12 month outcomes have improved only modestly and are often poor. Future focus on early depression and PTSD after concussive TBI appears warranted. Adverse outcomes are incompletely explained, however, and additional studies with prospective collection of data on acute injury severity and polytrauma, as well as reduced attrition before follow-up will be required to fully address the root causes of persistent disability after wartime injury.

Keywords: blast TBI; clinical outcomes; concussive TBI; PTSD

Introduction

THERE ARE MORE THAN 2 MILLION US military veterans of the recent conflicts in Iraq and Afghanistan.¹ It is estimated that 19% of this deployed force incurred a possible traumatic brain injury (TBI) in these wars.² Of clinician diagnosed TBIs across

both deployed and nondeployed US military personnel, 82.5% have been classified as mild TBI or concussion.^{1,3} The long-term clinical impact of these wartime injuries remains incompletely described.^{4,5} Most previous studies in active-duty US military personnel and veterans have been restricted to single cohort evaluations,^{6–15} often involving retrospective record review^{6–8} or self-report.^{9–13,15,16}

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As part of our efforts to assess the role of advanced magnetic resonance imaging (MRI) methods in the identification and assessment of the effects of concussive TBI in US military personnel,^{17,18} we obtained standardized, prospective, clinician rating-based outcome information 6–12 months after injury in four distinct cohorts of US military personnel between 2008 and 2013 using essentially identical methods across studies.^{19–21} This provided the opportunity to assess for trends in outcome over time. Our overarching goal was to analyze data across these cohorts to determine the relationship between global disability and clinical measures including neurobehavioral symptoms, neuropsychological performance, and psychiatric symptomatology.

During the course of our studies, the US military issued a Directive Type Memorandum (DTM 09-033) on June 21, 2010, with the objective to “identify, track and ensure the appropriate protection of service members exposed to potential concussive events, including blast events, to the maximum extent possible.”²² Before June 2010, TBI screening was not routinely implemented in Afghanistan or Iraq, and there were no standardized provisions for recurrent TBI prevention or treatment. Return-to-duty decisions were generally left to line commanders, not medical providers. Thus, many injuries were not immediately reported.² We therefore also used our data to compare clinical outcomes after concussive brain injury in military personnel injured in combat treated before and after the issuance of the DTM, although this was not a pre-specified goal of our research studies.

Methods

Study design

Analysis of four prospective, observational, longitudinal cohort studies.

Subjects

We screened a total of 1105 subjects between 2008 and 2013 across four cohorts and enrolled a total of 591 subjects, 347 of whom completed follow-up 6–12 months later at Washington University in Saint Louis (Fig. 1). The first three cohorts were enrolled at Landstuhl Regional Medical Center (LRMC) after medical evacuation from theater (Study 1–3). LRMC is the primary Role 4 evacuation hub for all medically evacuated casualties originating from Iraq and Afghanistan.

Study 1 cohort was enrolled from November 2008 to August 2009 and accepted patients 0–90 days post-injury. Study 2 cohort was enrolled from September 2010 to March 2011 and accepted patients 0–30 days post-injury. Study 3 cohort was enrolled from October 2010 to May 2013 and accepted patients 0–30 days post-injury. Study 4 cohort was enrolled at Kandahar Air Field and Camp Leatherneck in Afghanistan from March to September 2012 and accepted patients 0–7 days post-injury who remained in theater. Reasons for nonenrollment included contraindications to study procedures (399), refusal to participate (99), inability to follow up (5), interference with medical care (5), and other (6).

Four groups of subjects were enrolled:

- Blast control: subjects with blast exposure but without clinical evidence of resultant TBI
- Nonblast control: subjects without blast exposure and without TBI
- Blast + impact TBI: subjects with blast-plus-impact concussive TBI.
- Nonblast TBI: subjects with nonblast-related concussive TBI (i.e., TBI from mechanisms other than blast)

Inclusion criteria across cohorts for both the blast + impact and nonblast concussive TBI groups were as follows: (1A) a positive screen for TBI at LRMC based on standard US military clinical criteria²³ including self-report of blast exposure or no-blast mechanism such as blunt trauma resulting in loss of consciousness, amnesia for the event, or change in neurological status, for studies 1–3, or (1B) a clinical diagnosis of TBI in Afghanistan based on the criteria from the American Congress of Rehabilitation 1993, for Study 4; (2) TBI from blast or nonblast mechanisms of injury within the specified time of enrollment; (3) US military service member; (4) ability to provide informed consent in person; (5) no contraindications to MRI such as retained metallic fragments; (6) no pre-deployment history of moderate to severe TBI based on Department of Defense (DoD) criteria; (7) no pre-deployment history of major psychiatric disorder; (8) agreement to communicate by telephone or email monthly for 6–12 months and then travel to Washington University for in-person follow-up.

Inclusion criteria for the control groups were the same except for a negative diagnosis of TBI. The requirement for in-person informed consent made patients with more severe TBI typically not eligible, and none was enrolled. No intracranial abnormalities were detected on noncontrast head CT. Thus, all TBI subjects met the DoD criteria for uncomplicated “mild”/concussive TBI.

For the control groups in the LRMC cohorts who were medically evacuated, gastrointestinal, dermatological, and women’s health reasons were the main diagnoses. Orthopedic injuries from non-combat events such as broken bones resulting from recreational sports on time off or work-related accidents also comprised a subset of this population. The control group from Afghanistan mostly included onsite personnel who volunteered to participate in the study. A small number of controls enrolled in Afghanistan also had minor orthopedic injuries from noncombat events that did not require medical evacuation to LRMC. All clinical histories from the controls indicated no current or previous diagnoses of TBI. The blast control groups endorsed previous history of blast exposure but were found not to have had TBI after a clinical evaluation for possible brain injury at LRMC.

For the blast TBI groups across all of the cohorts, all available clinical histories indicated blast exposure plus another mechanism of head injury such as a fall, motor vehicle crash, or being struck by a blunt object. None suffered an isolated blast injury. The mechanisms of injury for the nonblast TBI group were primarily falls, motor vehicle crashes, or being struck by a blunt object that did not involve blast exposure. For both the blast and nonblast TBI groups, clinical histories indicated a change in the level of consciousness or loss of consciousness for at most a few minutes and post-traumatic amnesia for less than 24 h.

All clinical histories were verified by study personnel taking additional clinical history and reviewing medical records. All screening-based identifications of TBI were confirmed; none that screened positive for TBI were determined not to have had a TBI on further inspection. Initial records of clinical status in TBI subjects using the Military Assessment of Concussion Evaluation (MACE)²³ were reviewed. This brief cognitive test assesses orientation, immediate verbal memory, concentration, and short-term delayed verbal memory.

Protocol

The research protocol was approved by the Human Research Protection Office at Washington University, the Institutional Review Board at Brooke Army Medical Center, the Clinical Investigation Regulatory and Human Research Protection Offices of the U.S. Army Medical Research and Materiel Command, and the Department of Defense Central Command Medical Research and Materiel Command Institutional Review Board. Written informed consent was obtained from all subjects in person at the time of enrollment; no surrogate consent was allowed. Competence to

FIG. 1. Consort diagram of enrollment. *Subjects disqualified for poor performance on the Test of Memory Malingering and/or substantial artifacts on magnetic resonance imaging, criteria of the study. **Subjects disqualified at follow-up for apparent malingering and/or erratic performance on clinical evaluations. TBI, traumatic brain injury.

provide informed consent was assessed in a standardized fashion based on responses to questions regarding the purpose of the study, expected requirements for participation, and potential risks. Additional written consent was obtained from the subjects at the time of follow-up at Washington University. Active duty military subjects were not paid for participation, although travel expenses to Washington University were covered. Subjects not on active military duty status at the time of follow-up were paid \$240 plus travel expenses for participation.

Clinical assessments

Overall clinical outcome was assessed using the Glasgow Outcome Scale Extended (GOS-E).^{24,25} The GOS-E is scored from 1–8: 1 = dead, 2 = vegetative, 3–4 = severe disability, 5–6 = moderate disability, 7–8 = good recovery. Moderate disability (GOS-E = 5–6) is defined as one or more of the following: (1) inability to work to previous capacity; (2) inability to resume the majority of regular social and leisure activities outside the home; (3) psychological problems that have frequently resulted in ongoing family disruption or disruption of friendships. For subjects with moderate disability, we further subcategorized the disability as related to work, non-work, or both work and nonwork. Severe disability (GOS-E = 3–4) is defined as reduced ability to perform activities of daily living such that supervision is required. Standardized, structured interviews were performed according to published guidelines.²⁴

In-person clinical evaluations at Washington University included a neurobehavioral assessment, neuropsychological test battery, and psychiatric evaluation. The neurobehavioral assessment involved a structured examination and interview designed for patients with TBI (Neurobehavioral Rating Scale-Revised),²⁶ scored using a previously published five subdomain model.²⁷ The neuropsychological test battery consisted of the Conner's Continuous Performance Test II,²⁸ a computer-based assessment of attention, impulsivity, reaction time, and vigilance; the California Verbal Learning Test II,²⁹ an assessment of verbal declarative memory; the 25 hole grooved

pegboard test,³⁰ an assessment of upper extremity motor speed and coordination; a timed 25 foot walk; the Trail Making test,³¹ an assessment of visual scanning, coordination and mental flexibility; the Controlled Oral Word Association test,³² an assessment of verbal fluency; and the Wechsler Test of Adult Reading,³³ an estimate of pre-injury verbal intelligence. A relatively easy forced choice test embedded in the California Verbal Learning Test was used to assess adequacy of effort. Five subjects, all from Study 3, were disqualified for either poor effort or apparent malingering. The psychiatric evaluation included the Clinician-Administered Post-Traumatic Stress Disorder (PTSD) Scale (CAPS) for *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV)³⁴ and the Montgomery-Asberg Depression Rating Scale (MADRS)³⁵ performed by trained and validated clinicians. The CAPS was scored using standard scoring rules from Blake and colleagues, National Center for Post-traumatic Stress Disorder, July 1998 revision.

The 6–12 month follow-up evaluations involved approximately 5 h of in-person assessments. The standardized neurological examination and interview required approximately 1 h per subject. The psychiatric assessments required approximately 2 h per subject, and the neuropsychological battery required approximately 2 h per subject. Subjects took all medications as prescribed by their clinical providers. All tests were performed between 9 am and 5 pm in private, quiet, well-lighted rooms. All examiners were blinded to other clinical information, although in the course of the interviews, it often became clear whether the subjects were in the TBI or control group based on their endorsements of previous events. All examiners were clinicians who underwent standardized training in administering the assessments.

Safety and data monitoring

Subjects were assigned a random four-digit code number to protect confidentiality, and all research data were identified by code number only. A board certified psychiatrist (E. Nelson) was immediately available in case the CAPS examination exacerbated

PTSD symptoms. No exacerbations necessitating medical intervention occurred, although additional support from study staff was required on several occasions.

For clinical evaluations, the principal investigator audited 1 in 10 randomly selected subjects' data sets to ensure that data were scored and entered correctly. These audits revealed only minor discrepancies in scoring criteria that were then corrected across the entire cohort of subjects.

Statistical analyses

Data were analyzed using Statistica 12.0 (Statsoft Inc). The normal distribution of each continuous variable was assessed using the Shapiro-Wilk test. For normally distributed variables, Analysis of Variance (ANOVA), Analysis of Covariance (ANCOVA), and Student *t* tests were used to compare groups. For nonnormally distributed variables, Kruskal-Wallis tests and Mann-Whitney *U* tests were used. We pre-specified the hypothesis that subjects with concussive TBI would have worse outcomes than controls. One-sided tests were used when hypotheses were pre-specified, and two-sided tests were used otherwise. Uncorrected *p* values have been reported, but only considered significant if *p* < 0.05 after Bonferroni or Dunn correction for multiple comparisons.

After Dunn correction for multiple comparisons, there were no significant differences in GOS-E within comparable subgroups of subjects across studies. Therefore, the data were combined into the following three groups for additional analysis: nonblast control, blast control, concussive TBI. For ANCOVA and generalized linear models, there were too few officers (8 total) or women (10 total) for accurate statistical assessment, so the analyses were limited to enlisted men.

To determine the number of neuropsychological tests expected to be abnormal by chance, the binomial distribution was used with *p* = 0.02275 for the (*n* = 13) neuropsychological variables examined. Before this analysis, all neuropsychological variables were confirmed to be statistically independent as is required by the assumptions of this approach. There were no significant differences in the number of subjects with abnormal neuropsychological test performance in two or more neuropsychological assessments between evacuated TBI subjects, nonevacuated TBI subjects, and blast control subjects.

Logistic regression modeling was used to explore the relationship between a dichotomized measure of clinical outcome (GOS-E) and the demographic and clinical measures collected 6–12 months post-injury. For logistic regression, the Statistica 12.0 “generalized linear/nonlinear model building” algorithm was used with the selection of the “logit” link function for logistic regression. The algorithm generated a distinct model for each possible subset of demographic data and quantitative measures of specific symptoms and impairments. Models were then ranked by Akaike information criterion,³⁶ which penalizes models with larger numbers of parameters to discourage overfitting.

Results

Demographics of the subjects were consistent across all four cohorts from 2008–2013. Most subjects were young, high-school educated, male, enlisted members of the US Army (Table 1). In addition, demographics were consistent within groups comparing those who completed follow-up at 6–12 months and those who did not (Tables 2, 3).

TABLE 1. FOLLOW-UP PARTICIPANT CHARACTERISTICS

Characteristic	Study 1		Study 2		Study 3			Study 4	
	Blast control (n = 18)	Blast TBI (n = 47)	Blast TBI (n = 32)	Nonblast control (n = 69)	Blast control (n = 27)	Nonblast TBI (n = 29)	Blast TBI (n = 53)	Nonblast control (n = 34)	Blast TBI (n = 38)
Age in years:									
median (range)	32 (20–49)	26 (19–45)	24 (19–44)	31 (21–49)	34 (22–46)	28.5 (20–50)	26 (19–47)	28 (19–44)	26 (20–41)
Education in years:									
median (range)	13 (12–18)	12 (8–17)	12 (9–16)	14 (9–28)	13 (10–19)	14 (9–18)	12 (12–18)	15 (12–24)	13 (12–18)
Sex: no (%)									
Male	18 (100%)	47 (100%)	29 (91%)	63 (91%)	25 (93%)	26 (90%)	51 (96%)	27 (79%)	36 (95%)
Female	0	0	3 (9%)	6 (9%)	2 (7%)	3 (10%)	2 (4%)	7 (21%)	2 (5%)
Race/ethnicity: no (%) †									
White	15 (83%)	35 (74%)	22 (68%)	50 (73%)	20 (74%)	19 (60%)	40 (76%)	22 (65%)	29 (77%)
African American	2 (11%)	5 (11%)	5 (16%)	16 (23%)	4 (15%)	7 (27%)	4 (6%)	5 (15%)	2 (5%)
Hispanic/Latino	1 (6%)	2 (4%)	5 (16%)	3 (4%)	2 (7%)	3 (10%)	7 (14%)	7 (20%)	7 (18%)
Asian	0	5 (11%)	0	0	1 (4%)	1 (3%)	2 (4%)	0	0
Branch of service: no (%)									
US Army	15 (83%)	42 (89%)	26 (81%)	55 (80%)	24 (89%)	26 (90%)	46 (90%)	13 (38%)	32 (84%)
US Air Force	2 (11%)	0	0	11 (16%)	0	2 (7%)	1 (2%)	2 (6%)	0
US Marine Corps	1 (6%)	5 (11%)	5 (16%)	3 (4%)	3 (11%)	1 (3%)	5 (6%)	3 (9%)	6 (16%)
US Navy	0	0	1 (3%)	0	0	0	1 (2%)	16 (47%)	0
Military rank: no (%)									
Enlisted	16 (89%)	45 (96%)	32 (100%)	63 (91%)	24 (89%)	27 (93%)	52 (98%)	24 (71%)	35 (92%)
Officer	2 (11%)	2 (4%)	0	6 (9%)	3 (11%)	2 (7%)	1 (2%)	10 (29%)	3 (8%)
Theatre of operation: no (%)									
Afghanistan	6 (33%)	28 (60%)	27 (84%)	55 (80%)	21 (78%)	18 (62%)	50 (94%)	34 (100%)	38 (100%)
Iraq	12 (69%)	19 (40%)	5 (16%)	14 (20%)	6 (22%)	11 (38%)	3 (6%)	0	0

TBI, traumatic brain injury.

Scores on the MACE completed after medical evacuation to LRMC or directly after injury in Afghanistan did not significantly differ across studies within concussive TBI groups (Fig. 2A, $p=0.87$ Kruskal-Wallis ANOVA). Further, there were no trends in MACE as a function of date of injury (Fig. 2B, $p=0.52$ linear regression). Injury severity scores were not systematically collected for subjects enrolled at LRMC. All injury severity scores for subjects enrolled in Afghanistan were zero, meaning there were no apparent injuries to the head and neck, face, chest, abdomen, extremities, or general body as scored by a clinician.

Global outcomes

Global outcomes at 6–12 month follow-up assessed using the GOS-E significantly differed by group (Fig. 3A, $p<0.0001$ Kruskal-Wallis ANOVA). Subjects with concussive TBI had significantly worse outcomes than both the nonblast control subjects ($p<0.0001$) and blast controls ($p<0.0001$, one-sided Mann-

Whitney U tests). The blast control subjects exhibited significantly worse outcomes than nonblast control subjects ($p=0.0044$, two-sided Mann-Whitney U). The percentage of subjects who had an overall outcome of moderate to severe disability ranged from 62–96% in the TBI cohorts.

For most cohorts, the majority (70–82%) of injured subjects with moderate disability had disability from a combination of work and nonwork factors (Fig. 3B). The exception was for the most recent study cohort involving subjects enrolled in Afghanistan (Study 4) in which 52% of those with moderate disability had nonwork disability only. A minority of injured subjects (6–12%) had work-related disability only.

Neurobehavioral assessment

Neurobehavioral impairment assessed using the Neurobehavioral Rating Scale-Revised also differed significantly by group (Fig. 4A, $p<0.0001$ Kruskal-Wallis ANOVA). Subjects with concussive TBI exhibited significantly worse neurobehavioral impairments than both nonblast controls ($p<0.0001$) and blast controls ($p=0.001$, one-sided Mann-Whitney U tests). Blast controls were more impaired than nonblast controls ($p<0.0001$, two-sided Mann-Whitney U test). Impairments were noted in each of the five subdomains: mood/affect, executive/cognitive function, oral/motor function, positive symptoms, and negative symptoms (Fig. 4B–F; all $p<0.0001$, Kruskal-Wallis ANOVA).

Neurobehavioral impairments among subjects with concussive TBI were less severe for those injured after June 21, 2010, than for those injured before the issuance of the DTM (Fig. 4G, $p=0.017$, Mann-Whitney U test). The significance was marginal ($p=0.057$, ANCOVA) when including the following covariates: age, education, branch (Army vs. other), race (white vs. other), mechanism of injury (blast vs. nonblast), and evacuation to LRMC vs. treatment in Afghanistan with return to duty. None of the covariates individually were significantly associated with neurobehavioral impairment. Further, there was a trend toward less severe neurobehavioral impairment after concussive TBI as a function of date of injury (Fig. 4H). Average impairments decreased by 1.1 points of 87 per year (95% confidence interval from 0.4–1.8 points) from 2008–2013 ($r^2=0.04$, $p=0.0037$, linear regression). This trend lost statistical significance, however, when including the covariates in the statistical model ($p=0.08$, generalized linear model).

Neuropsychological testing

Across cohorts, concussive TBI groups generally performed similarly to controls on neuropsychological testing (Table 4). Evaluation at the single-subject level revealed subsets of subjects with concussive TBI with impaired neuropsychological performance (Fig. 5). Abnormal performance on each individual assessment was defined as a subject's score that fell outside two standard deviations worse than the mean of the pooled non-blast control group for that examination. For each subject, the number of tests with abnormal performance was then summed. The number of subjects per group was then compared with what would be expected by chance. More subjects with abnormal test performance in two or more neuropsychological assessments than expected by chance were observed in the evacuated TBI subjects from Studies 1–3 (51/161, 31%, $p=0.00001$), the nonevacuated TBI subjects from Study 4 (10/38, 26%, $p=0.003$), and blast control subjects (10/45, 22%, $p=0.01$, chi-square tests). There were no differences between subjects injured before versus after the issuance of the DTM

FIG. 2. Military Assessment of Concussion Evaluation (MACE). Lower scores indicate greater concussion impairment (Max 30, Symptomatic defined as below 25 on any assessment²³). (A) No difference in MACE between cohorts ($p=0.87$ Kruskal-Wallis analysis of variance). (B) No trends in MACE as a function of date of injury ($p=0.52$, linear regression). Note that MACE was not performed in controls. TBI, traumatic brain injury. Color image is available online at www.liebertpub.com/neu

FIG. 3. Global Outcome. (A) Glasgow Outcome Scale–Extended (GOS-E). Percent of service members with moderate to severe disability are reported under each study group on the graph. (B) Subgroup disability for service members with GOS-E score of 6 or less. CTL, control; TBI, traumatic brain injury. Color image is available online at www.liebertpub.com/neu

($p=0.87$) and no trends in neuropsychological test abnormalities after concussive TBI as a function of date of injury ($p=0.53$).

Performance on three tests was significantly different across studies by Kruskal-Wallis ANOVA after correction for multiple comparisons. This included a timed 25-foot walk ($p=0.0001$); the 25-hole grooved pegboard test ($p=0.00001$), an assessment of upper extremity motor speed and coordination; and the Controlled Oral Word Association test ($p=0.001$), an assessment of verbal fluency. For each assessment, the nonblast control subjects from Studies 3 and 4 outperformed blast control subjects and the medically evacuated concussive TBI groups from Studies 1–3. There were no significant differences after Dunn correction for multiple comparisons between the nonblast controls and nonmedically evacuated concussive TBI group from Study 4. Likewise, there were no significant differences between blast controls and concussive TBI groups.

PTSD and depression

Clinician ratings of depression and PTSD severity substantially differed across groups (Fig. 6, $p<0.0001$, Kruskal-Wallis ANOVA).

Subjects with concussive TBI were more depressed than both nonblast control ($p<0.0001$) and blast control ($p=0.0062$, one-tailed Mann-Whitney U tests) subjects. Blast controls also had more depression than nonblast controls ($p=0.0007$, two-tailed Mann-Whitney U test). Similarly, subjects with concussive TBI also had more severe PTSD than both nonblast controls ($p<0.0001$) and blast controls ($p=0.0004$, one-tailed Student t tests). Blast controls also had more severe PTSD than nonblast controls ($p<0.0001$, two-tailed Student t test). All three PTSD domain subscores (re-experiencing, avoidance and numbing, hyperarousal) were found also to be significantly different across groups, as was self-reported sleep deprivation (Fig. 7, $p<0.0001$ Kruskal-Wallis ANOVAs).

For the poor sleep index, the concussive TBI groups were not collapsed because blast TBI subjects from Study 1 differed significantly from blast TBI subjects in Study 4 ($p<0.05$, Dunn Multiple Comparison Test). Both nonblast control groups were pooled and both blast control groups were pooled, however, because these did not differ from each other. With this pooling, the overall ANOVA was again significant ($p<0.0001$). In *post hoc* testing, blast + impact concussive TBI subjects from Studies 1 and 2 had higher poor sleep indexes than nonblast controls ($p<0.05$), but none of the TBI groups differed from

FIG. 4. Neurobehavioral Rating Scale and subdomains. (A) Neurobehavioral outcome assessed using the Neurological Rating Scale-Revised (NRS) total score: (Max 87, higher scores indicate worse outcomes). Results assessed 6–12 months after enrollment. (B) Mood/affect domain (Max 15). (C) Executive/cognitive domain (Max 24). (D) Oral/motor domain (Max 12). (E) Positive Symptoms domain (Max 21). (F) Negative Symptoms domain (Max 12). Higher scores on all of the measures indicate worse impairment. All $p < 0.0001$, Kruskal-Wallis analysis of variance. (G) Worse neurobehavioral outcomes before the issuance of the Directive Type Memorandum (DTM) on 6/21/10 compared with afterward in subjects with concussive TBI ($p = 0.017$, Mann-Whitney U test, $p = 0.057$ analysis of covariance including covariates). (H) Trend toward reduced neurobehavioral impairment over time in subjects with concussive TBI ($p = 0.0037$ linear regression, $p = 0.08$ generalized linear model including covariates). CTL, control; TBI, traumatic brain injury. Color image is available online at www.liebertpub.com/neu

the blast controls. The blast control group was not statistically significantly different from the nonblast control group.

Among subjects with concussive TBI, both depression and PTSD were less severe for those injured after the issuance of the DTM than before (Fig. 6 C,D, $p = 0.02$ for depression, $p = 0.006$ for PTSD, Mann-Whitney U tests). The statistical significance, however, was lost ($p = 0.12$ for depression, $p = 0.07$ for PTSD, ANCOVA) when including the covariates. Evacuated TBI subjects (Studies 1–3) had more severe PTSD than nonevacuated (Study 4) subjects ($p = 0.03$) in this analysis (Fig. 6B). There were trends toward less severe depression and PTSD as a function of date of injury (Fig. 6 E,F). Depression decreased by 1.6 points (95% confidence interval, 0.4–2.8 points) of 60 and PTSD decreased by 5.9 points (95% confidence interval, 2.8–9.0 points) of 136 (–4.3%) on average per year from 2008–2013 ($r^2 = 0.035$, $p = 0.012$ for depression, $r^2 = 0.069$, $p = 0.00037$ for PTSD, linear regression). The trend for depression lost significance

($p = 0.15$), but the trend for PTSD maintained statistical significance when including the covariates ($p = 0.03$, generalized linear models).

Among blast controls, there were no differences in depression ($p = 0.59$) or PTSD ($p = 0.42$) for those enrolled after versus before the issuance of the DTM. Likewise, there were no trends in depression ($r^2 = 0.0087$, $p = 0.52$) or PTSD ($r^2 = 0.003$, $p = 0.72$) as a function of date of first evaluation.

Multivariate correlates of dichotomized global outcome

Dichotomized global outcome was defined as follows: GOS-E scores of 7–8 were categorized as good outcome, and scores of ≤ 6 were defined as disabled. Candidate variables for logistic regression modeling included PTSD severity (CAPS total score), depression severity (MADRS), self-reported sleep deprivation, group distinction (control vs. TBI), exposure (blast vs. nonblast),

TABLE 4. NEUROPSYCHOLOGICAL TEST PERFORMANCE

<i>Test</i>	<i>LRMC 1</i>		<i>LRMC 1E</i>		<i>LRMC 2</i>		<i>AFG</i>		
	<i>Blast CTL</i> (n = 18)	<i>Blast TBI</i> (n = 47)	<i>Blast TBI</i> (n = 32)	<i>Nonblast CTL</i> (n = 69)	<i>Blast CTL</i> (n = 27)	<i>Nonblast TBI</i> (n = 29)	<i>Blast TBI</i> (n = 53)	<i>Nonblast CTL</i> (n = 33)	<i>Blast TBI</i> (n = 38)
25-Foot Walk (seconds) (<i>Motor Strength, Balance, Coordination</i>)	5.18 ± 2.05	4.96 ± 1.02	4.65 ± 1.37	3.92 ± 0.82	4.22 ± 0.66	4.76 ± 1.16	4.59 ± 1.17	3.78 ± 0.60	4.23 ± 0.70
Conners' Continuous Performance Test II									
Omission Errors (T-score): (<i>Attention Lapses</i>)	54.49 ± 21.18	51.39 ± 12.56	75.67 ± 64.71	48.29 ± 12.17	47.45 ± 7.51	53.30 ± 15.11	56.06 ± 19.8	48.85 ± 10.51	60.41 ± 28.13
Commission Errors (T-score): (<i>Impulsivity</i>)	50.92 ± 10.54	51.73 ± 9.64	55.36 ± 8.85	50.40 ± 10.60	50.02 ± 8.19	52.46 ± 9.81	54.05 ± 10.6	53.83 ± 11.03	54.70 ± 10.16
Hit Rate (T-score): (<i>Reaction Time</i>)	49.4 ± 11.22	47.69 ± 9.04	47.88 ± 12.80	48.94 ± 11.72	48.98 ± 8.67	52.10 ± 12.22	47.83 ± 8.63	46.06 ± 9.88	50.81 ± 10.33
Hit Rate Block Change (T-score): (<i>Sustained Vigilance</i>)	52.62 ± 10.29	52.17 ± 10.74	49.92 ± 13.73	52.05 ± 10.62	48.01 ± 8.82	51.64 ± 13.75	48.73 ± 12.0	48.67 ± 5.56	54.69 ± 13.43
Wechsler Test of Adult Reading (Standard Score)	97.56 ± 12.56	98.3 ± 11.74	100.09 ± 10.48	102.88 ± 14.55	100.56 ± 10.99	98.52 ± 11.10	99.49 ± 11.66	105.41 ± 10.58	99.03 ± 12.50
(<i>Estimate of Pre-injury Verbal Intelligence</i>)									
California Verbal Learning Test II									
Long-Delay Free Recall (Standard Score)	0 ± 0.89	-0.13 ± 0.94	-0.33 ± 1.31	-0.17 ± 1.10	-0.15 ± 0.95	-0.32 ± 1.27	-0.58 ± 1.21	0.15 ± 1.28	-0.57 ± 0.92
(<i>Verbal Memory</i>)									
Total Intrusions (Standard Score)	0.44 ± 1.45	0.15 ± 1.04	0.28 ± 1.10	0.22 ± 1.00	0.22 ± 0.95	0.52 ± 1.42	0.45 ± 1.38	0.14 ± 0.84	0.50 ± 1.22
(<i>Falsely Recalled Items</i>)									
List B vs. Trial 1 List A (Standard Score)	0.11 ± 1.13	-0.34 ± 1.11	-0.23 ± 1.16	0.08 ± 0.87	-0.15 ± 0.89	0.58 ± 1.03	-0.16 ± 1.12	0.00 ± 1.05	-0.12 ± 0.90
(<i>Proactive Memory Interference</i>)									
Grooved Pegboard (<i>Motor Speed & Coordination</i>)									
Average Dom & Non-Dom Time (seconds)	80.94 ± 11.54	77.31 ± 12.65	78.72 ± 14.28	69.03 ± 17.7	69.04 ± 10.56	75.84 ± 15.85	75.54 ± 15.52	67.68 ± 10.34	71.63 ± 7.74
Trail Making Test									
Trails A time (seconds) (<i>Visual Scanning, Coordination</i>)	24.78 ± 5.86	27.28 ± 10.54	28.02 ± 11.28	22.10 ± 8.61	24.26 ± 7.41	26.57 ± 14.10	28.5 ± 16.69	23.24 ± 7.65	23.6 ± 7.08
Trails B time (seconds) (<i>Trails A + Mental Flexibility</i>)	59.56 ± 15.80	66.79 ± 22.53	63.06 ± 19.01	57.12 ± 24.77	57.00 ± 14.97	67.52 ± 31.28	61.19 ± 21.40	55.38 ± 18.65	64.43 ± 23.89
Controlled Oral Word Association Total Score: (Verbal Fluency)	34.33 ± 7.35	35.91 ± 9.31	34.19 ± 9.53	42.1 ± 10.18	40.37 ± 9.05	37.62 ± 9.98	37.75 ± 9.30	42.82 ± 9.61	41.45 ± 11.47

LRMC, Landstuhl Regional Medical Center; AFG, Afghanistan; CTL, control; TBI, traumatic brain injury.

All data reported as mean ± standard deviation.

*Significant group differences by Kruskal-Wallis analysis of variance after Bonferroni correction for multiple comparisons.

FIG. 5. Neuropsychological testing abnormalities. The number of subjects with neuropsychological test abnormalities are displayed by group in comparison with what would be expected by chance (blue bars). Percent of subjects is displayed to account for the differences in the number of subjects in each group. Dotted box indicates the group of subjects who had poor performance on 2 or more of the 13 neuropsychological variables. TBI, traumatic brain injury; StDev, standard deviation. Color image is available online at www.liebertpub.com/neu

FIG. 6. Post-traumatic stress disorder (PTSD) and depression severity. (A) Depression severity assessed by the Montgomery-Asberg Depression Rating Scale (MADRS) (Max 60). (B) PTSD severity assessed by the Clinician Administered PTSD Scale for *Diagnostic and Statistical Manual of Mental Disorders, 4th edition* (CAPS) (Max 136). Dotted lines indicate the threshold for moderate to severe symptomatology for each evaluation. (C) Worse depression before the issuance of the Directive Type Memorandum (DTM) compared with afterward in concussive subjects with traumatic brain injury (TBI) ($p=0.02$, Mann-Whitney U test, $p=0.12$ analysis of covariance [ANCOVA] including covariates). (D) Worse PTSD before the issuance of the DTM compared with afterward in subjects with concussive TBI ($p=0.006$, Mann-Whitney U test, $p=0.07$ ANCOVA including covariates). (E) Trend toward reduced depression over time in subjects with concussive TBI ($p=0.012$ linear regression, $p=0.15$ generalized linear model). (F) Statistically significant reduction in PTSD over time in subjects with concussive TBI ($p=0.00037$ linear regression, $p=0.03$ generalized linear model including covariates). CTL, control. Color image is available online at www.liebertpub.com/neu

FIG. 7. Subdomains of the Clinician Administered Post-traumatic Stress Disorder Scale (CAPS) for *Diagnostic and Statistical Manual of Mental Disorders, 4th edition*. (A) CAPS B Severity – Re-experiencing (Max 40). (B) CAPS C Severity – Avoidance and Numbing (Max 56). (C) CAPS D Severity – Increased Arousal and Hypervigilance (Max 40). (D) Poor sleep index, defined as the self-reported number of desired hours of sleep minus the number of hours reported taken from subsection D-1 of the CAPS. Higher scores on all of the measures indicate worse impairment. All $p < 0.0001$, Kruskal-Wallis ANOVA. Color image is available online at www.liebertpub.com/neu

enrollment site distinction (evacuated vs. nonevacuated), age, education, number of neuropsychological test abnormalities, date of enrollment, and enrollment before versus after the issuance of the DTM. Many subjects injured after the issuance of the DTM were evacuated from theater as late as May 2013, so the enrollment site distinction and date of enrollment were not redundant.

The best logistic regression contained the CAPS, MADRS, group distinction (control vs. TBI), and enrollment site distinction (evacuated vs. nonevacuated) with a receiver operating characteristic area under the curve of 0.8351 (Fig. 8). Higher likelihood of disability was observed in service members with diagnoses of concussive TBI, those who were evacuated, and those who had more severe PTSD and depression. Date of enrollment and enrollment before versus after the issuance of the DTM did not contribute to the best model of global outcome.

Discussion

In summary, there were adverse clinical outcomes 6–12 months after concussive TBI in a substantial majority of US military personnel injured in theater. Outcomes were generally consistent across four cohorts enrolled from 2008–2013, although there were modest improvements in PTSD severity over time. Blast-exposed service members without apparent TBI had outcomes that were intermediate between subjects with concussive TBI and nonblast-exposed military controls. Adverse global outcomes were typically in both work- and nonwork-related domains. Overall disability was most strongly associated with concussive TBI diagnosis, PTSD and depression severity, and requirement for medical evacuation from theater.

The percentage of subjects with concussive TBI with poor overall outcome at 6–12 months (62–96%) far exceeds what is routinely reported in the civilian literature for concussive TBI patient populations even with polytrauma where reports range from 22–47%.^{37,38} Blast-related mechanisms causing TBI do not appear to be a major contributor, because subjects with nonblast-related TBI fared comparably.^{20,21} Nonmutually exclusive possible explanations include (1) the severities of injuries were substantially greater in the military subjects, and (2) the context and recovery from military service-related TBI differs fundamentally from civilian TBI.

This is the first study to our knowledge to compare outcomes before and after issuance of the DoD DTM 09-033 in 2010 regarding identification and treatment of military concussive TBI in theater.²² While such an evaluation was not our pre-specified purpose, these four longitudinal cohorts assessed in a homogenous fashion over 5 years provided a serendipitous opportunity to do so. Our data, however, in no way reflect the efficacy of the DTM with regard to its stated purpose and should not be interpreted as such. Further, none of our data directly bear on the question of the extent to which the specific provisions in the DTM were actually followed.

The results from our study fit well with those of the recently reported prospective longitudinal Marine Resiliency Study.³⁹ In the Marine Resiliency Study, subjects with deployment-related TBI had increased PTSD severity 3 months after deployment, especially in participants with less severe pre-deployment PTSD symptoms. Global disability was not reported in the Marine Resiliency Study, however. Although dates of enrollment spanned 2008–2012, analysis of outcomes as a function of time were not presented.

One of the most striking findings in this report is that over a 5-year period from 2008 to 2013, the severity of disability, PTSD, and depression after concussive TBI in deployed US military personnel improved only marginally. A reasonable conclusion from our result could be that more effective interventions to treat those with PTSD

FIG. 8. Correlates of global outcome. (A) Receiver-operator curve and parameter table for best fit logistic regression model of overall disability, defined by the dichotomized Glasgow Outcome Scale–Extended (GOS-E) with 7 or 8 categorized as good outcome and GOS-E 6 or below categorized as disabled. The best model by Akaike information criterion contained the Clinician Administered Post-traumatic Stress Disorder Scale [PTSD] CAPS score (PTSD severity), Montgomery-Asberg Depression Rating Scale (MADRS) score (depression severity), injury group distinction (traumatic brain injury [TBI] vs. control), and enrollment site distinction (subjects requiring medical evacuation vs. those who did not require medical evacuation).

and depression in this setting should be considered a top priority. Such interventions were not a part of the DTM, although an assessment of acute stress disorder is a mandatory element of the comprehensive neurological evaluation performed in those who have had three or more documented concussions within a 12-month period. Pre-injury resilience training and interventions starting at very early times after concussive TBI in high-risk persons, such as military service members, could be effective strategies. The extent to which the specific act of medical evacuation that caused the service members to leave the support of their units contributed to more severe PTSD and depression remains to be determined.

In other contexts, both PTSD and depression are at least partially treatable with a combination of medications^{40–43} and psychological interventions such as prolonged exposure^{44–46} or cognitive processing therapy.^{45,47} No additional clinical care was provided as part of these research studies, and we did not collect data on the specific interventions the study participants received. Recent literature, however, indicates that only a relatively small fraction of US military service members complete a full course of treatment for PTSD and depression. Reasons cited include lack of access, fear of stigma, poor follow-up compliance, and initial worsening of symptoms during the early part of the therapy. Likewise, reasons for less than ideal pharmacotherapy effectiveness include troubling side effects, irregular compliance, and concomitant drug or alcohol use.^{2,43,48–52} Anecdotal reports obtained from the participants in our cohorts are in line with the above cited concerns.

Alternatively, it is possible that the effects of these standard treatments for PTSD and depression are less effective in the context of TBI because of brain circuitry disruption and neurochemical deregulation. Thus, based on the results presented here, a logical direction for future studies would involve assessment of the efficacy of both established and novel therapeutic approaches to PTSD and depression in patients with TBI. Given the substantial burden of TBI, PTSD, and depression in military service members and veterans who have volunteered for deployment to war zones, maximal efforts to improve outcomes are warranted.

Strengths of this study include the use of a prospective, observational, longitudinal cohort design; enrollment of all combat-deployed, active-duty US military; the inclusion of subjects with

both blast-related and nonblast-related concussive TBI; the assessment of both blast-exposed and nonblast-exposed combat-deployed controls; the incorporation of both medically evacuated and nonmedically evacuated casualties; and the comparison of four independent cohorts of subjects across all branches of the military.

Nonetheless, there are several limitations that should be acknowledged: (1) unknown diagnostic accuracy for concussive TBI in the absence of an objective standard at the various sites and times of enrollment; (2) self-report for several of the key outcome measures including overall disability; (3) heterogeneous treatment across centers in theater and in the US after injury; (4) single time point for most assessments; (5) incomplete assessment of combat exposure severity; (6) no objective markers of the severity of initial injury (Glasgow Coma Scores were not available, although initial MACE scores showed no trends over time. Injury severity scores were not always available, although they were uniformly zero in subjects enrolled in Afghanistan), (7) possible unmeasured covariates that differ between groups such as medical comorbidities; (8) moderately large dropout after enrollment but before final evaluation—38% (122/321) of TBI subjects and 42% (106/254) of controls—raising the question of selection bias; (9) the possibility that outcome rater bias could have been introduced based on clinical presentation; and (10) lack of long-term follow-up.

We did not formally assess the interrater reliability of the Glasgow Outcome Scale. The Glasgow Outcome Scale, neurobehavioral rating scale, neuropsychological testing, and PTSD/depression ratings, however, were performed by independent evaluators without knowledge of injury status or of the findings of the other assessments. Thus, the correlations between measures indicates at least moderate reliability.

In determining overall disability, we followed the instructions laid out in the article by Wilson and associates²⁴ in 1998, which state: “Disability must be a result of mental or physical impairment” and more explicitly “...if a patient is capable of performing the activity but does not do it for some reason they are not considered disabled.” Thus, the relatively high rate of general unemployment in the United States because of economic concerns during the time of the study did not influence our findings.

It is unclear whether 6–12-month outcomes are truly representative of long-term function or quality of life.^{53–57} Studies are currently under way to explore >5 year outcomes in these military concussive TBI cohorts.

Based on these data, it appears that the severity of PTSD and depression are strongly linked to overall outcomes after concussive TBI in US service members. The direction of causality, however, cannot be determined from the current results. In our view, the most likely scenario is that concussive TBI along with the trauma-associated psychopathology (i.e., PTSD, depression) that accompanies deployment in a war zone interact in a synergistic fashion to worsen outcomes; TBI may damage the brain's emotional regulation circuitry, and the trauma-associated psychopathology may interfere with recovery from TBI. It is also possible, however, that the overall TBI severity is the primary driver of both overall outcomes and trauma-associated psychopathology. A third alternative is that the most stressful wartime events that caused the most persistent and severe PTSD and depression also caused acute amnesia or transient changes in awareness, and were therefore incorrectly labeled as concussive TBI. Clearly, future studies involving objective measures of primary brain injury severity and careful anatomical delineation of the relevant brain circuitry involved in emotional regulation will be required to address these alternatives.

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Author Disclosure Statement

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