Patterns of Early Emotional and Neuropsychological Sequelae after Mild Traumatic Brain Injury

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Abstract

Although mild traumatic brain injury (mTBI) is now recognized as a major health issue, there have been relatively few studies of its acute effects. Previous studies of mTBI assessed at 1 week or less post-injury have produced inconsistent results, spanning reports of no ill effects to findings of robust dysfunction. These gross disparities reflect study differences such as the criteria for mTBI diagnosis and selection of comparison groups. In consideration of these issues, this study investigated outcome in the first 96 hours after injury in adolescents and adults ages 12–30 years with mTBI ($n=73$) compared with orthopedically injured (OI, $n=65$) and typically developing controls (TDC, $n=40$). The mTBI group reported significantly greater general psychological distress, post-concussion symptom severity, and post-traumatic stress severity than OI (all $p<0.0001$) and TDC (all $p<0.0001$); the OI and TDC groups responded similarly on these variables. There was a significant Group $\times$ Age interaction on the Total score ($p<0.009$), and the Cognitive ($p=0.01$) and Somatic ($p<0.032$) subscales of the Rivermead Post Concussion Symptoms Questionnaire where increasing symptom severity was associated with increasing age in the mTBI group. On neuropsychological assessment, the mTBI group performed significantly more poorly compared with OI for Verbal Selective Reminding Test (delayed recall, $p=0.0003$) and Symbol-Digit Modalities Test (SDMT written $p=0.03$; oral, $p=0.001$). The TDC group more robustly outperformed the mTBI group on these measures and also on the Brief Visuospatial Memory Test (delayed recall, $p<0.04$), Letter Fluency ($p<0.02$), and Category Switching ($p<0.04$). The TDC group outperformed the OI group on SDMT and Letter Fluency. These findings are consistent with previous reports of acute deficits in episodic memory and processing speed acutely after mTBI. Notably, however, these data also demonstrate the challenges of comparison group selection because differences were also found between the TDC and OI groups.

Key words: memory; mild traumatic brain injury; post-concussion syndrome; post-traumatic stress disorder; processing speed

Introduction

TRAUMATIC BRAIN INJURY (TBI) is a significant public health concern in the United States because it is one of the most common neurologic disorders¹ with an estimated incidence of 1.7 million annually.² More than 75% of these TBIs are classified as mild TBI (mTBI),³ and nearly 80% of all patients with TBI are treated and released from an Emergency Department (ED).² As a major health issue, the economic costs of mTBI have been estimated at \$16.5 billion.⁴ The direct costs of lost productivity and the indirect costs of burden placed on family and friends and the de-

creased quality of life for the person with mTBI, however, have not been clearly established.

Previous investigations of acute mTBI within the first week post-injury have been scarce (relative to the number of outcome studies conducted 1 month or longer post-injury), and findings have likely varied, in part, from heterogeneous pathophysiology and other confounding variables. Criticisms of these studies and potential sources of inconsistency of findings have included the use of differing definitions of mTBI,^{5,6} use of differing inclusion and exclusion criteria, use of retrospective designs, or unrepresentative convenience samples,⁷ differing comparison groups, widely

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varying assessment domains and instruments,⁸ small sample sizes, and failure to adequately screen for potentially confounding pre-existing conditions.⁸

For example, although reported as sustaining moderate TBI severity "...who would normally be included in the category of minor head injuries," McMillan and Glucksman⁹ found that at 1 week post-injury, these patients performed no differently than a group of orthopedic controls on tests of visual and verbal memory and ratings of post-concussion syndrome (PCS) symptom severity. There were, however, significant differences on subjectively rated memory problems and a task of speeded working memory (i.e., Paced Auditory Serial Addition Test—PASAT).

Lidvall and associates¹⁰ found no differences between patients with mTBI who had PCS versus no PCS at 2, 6, or more days after injury on all measures of cognition used. Similarly, Newcombe and colleagues¹¹ found no evidence of dysfunction when comparing hospitalized patients with minor head injury to orthopedic and minor surgery controls on tasks of memory, speeded working memory, and executive function 48 h post-injury. In one of the larger studies reviewed, Ponsford and coworkers¹² assessed 84 patients who met the American Congress of Rehabilitation Medicine criteria¹³ for mTBI at 1 week post-injury. Compared with a group of patients from the ED with minor injuries, the mTBI group performed poorly on measures of auditory attention and working memory (Digit Span and Digit Symbol), the Speed of Comprehension test, and on a measure of PCS symptoms, but not on other tests found sensitive to mTBI including the PASAT, reaction time tests, or verbal memory (i.e., Rey Auditory Verbal Learning Test where the mTBI group actually performed better than the controls).

In contrast to these studies with mostly negative findings, others have reported significant early effects of mTBI. For instance, MacFlynn and colleagues¹⁴ assessed 45 patients with "minor closed head injury" within 24 h post-injury and found that they performed significantly worse compared with "general practice" patients on a four-choice reaction time test. In a three-center study that recruited groups of paid volunteers matched on age, race, and education, Levin and associates¹⁵ reported that hospitalized patients with mTBI (i.e., Glasgow Coma Scale [GCS] score 13–15 without neurologic complications or neurosurgical procedures) performed significantly worse on speeded working memory (Paced Auditory Serial Addition Test and Digit Symbol), auditory attention (Digit Span), and measures of verbal and visual memory when tested 1 week post-injury. Levin and associates¹⁵ also administered a structured interview to assess post-concussion symptoms and found that the patients with mTBI had significantly higher cognitive, somatic, and affective symptom scores than uninjured subjects at each of the three centers.

When tested at 72 h post-injury, a group with "mild concussions" without hospitalization performed significantly more slowly on a measure of complex reaction time than paid volunteers matched on age, sex, and education.¹⁶ In a very small study of hospitalized patients with mTBI (GCS 13–15), Brooks and coworkers¹⁷ reported that at 2–3 days post-injury, the mTBI group was significantly outperformed by matched controls on measures of verbal fluency (Controlled Oral Word Association Test), visual tracking and attention (Trail Making Test), and speeded working memory (PASAT).

More recently, the literature has rapidly expanded in the area of sports concussion. One advantage of studying sports players is the ability to obtain pre-season baseline assessments of neurocognitive performance to more precisely assess dysfunction after concussion/mTBI. This is not without its own issues, including performance

differences in group versus individual pre-season testing,¹⁸ which is a concern as more assessments gravitate toward group administration of computer-based testing for improved economies of scale, and the motivation of players to underperform at baseline so as to minimize the effects of possible future concussions enabling them to return to play earlier. Although important and well-deserving of greater scrutiny, these issues are beyond the scope of this study, and the following brief review focuses on the acute effects of sports concussion, *per se*.

In a study of 10 professional rugby players and 10 matched uninjured athletes, Hinton-Bayre and associates¹⁹ found that at 24–48 h post-injury, concussed athletes demonstrated significant dysfunction on the Symbol-Digit Modalities Test (SDMT), Speed of Comprehension, and Digit Span. In a somewhat larger follow-up study, Hinton-Bayre and colleagues²⁰ essentially replicated their previous findings, but also found that while most players (80%) were impaired 1–3 days post-injury, some players (35%) did not return to baseline performance until 3–5 weeks post-injury.

Using the Standardized Assessment of Concussion (SAC), McCrea and coworkers²¹ studied high school and college athletes immediately and 48 h after a grade 1 concussion. Although significant declines from pre-season scores were found immediately after injury, these differences resolved by 48 h post-injury. Similarly, McCrea and colleagues²¹ found that college football players assessed with the SAC immediately, 3 h, and daily up to 5–7 days post-injury demonstrated significant performance reductions for cognitive and balance measures, and increased PCS symptoms had resolved by 5–7 days post-concussion.

High school athletes assessed on a computerized assessment tool (ImPACT) at 36 h, and 4 and 7 days post-injury demonstrated significant declines on the memory composite score compared with uninjured athletes and with pre-season performance that persisted until 7 days after injury while self-report of PCS symptoms resolved within 4 days.²² Lovell and associates²³ also studied high school athletes sustaining a grade 1 concussion and found that this group demonstrated significant reductions in memory and increased PCS symptoms 36 h post-injury using the ImPACT. Similar findings were reported by Iverson and colleagues²⁴ using the ImPACT with athletes having sustained multiple concussions assessed within 5 days of the index injury.

Using criteria of the American Academy of Neurology (AAN) to grade concussion, Erlanger and coworkers²⁵ assessed high school and college-level football and hockey players at 1–2 day intervals using an Internet-based assessment (Concussion Resolution Index, HeadMinder) beginning on the day of injury until symptoms resolved. They found that all athletes demonstrated significant cognitive slowing on one or more speed indices 2–3 days post-injury.

Age appears to be a significant factor in adolescents and young adults. Field and associates²⁶ reported that high school athletes with AAN grade 1 concussions performed significantly worse than age-matched controls 7 days post-injury (on measures including Hopkins Verbal Learning Test-Revised and Brief Visuospatial Memory Test-Revised) [BVM-T-R] whereas college athletes performed similarly to matched controls by 3 days post-injury. In a study of elite, non-professional Australian-rules football players, concussed players were assessed until symptoms resolved. In 78 players, symptoms lasted an average of 48.6 h, and they also demonstrated impaired performance on the Trail Making Test and Digit Symbol; however, computerized testing indicated cognitive performance reductions lasted 2–3 days later. Overall, patients sustaining sports-related concussions appear to be younger and recover more quickly than non-sports-related injuries (e.g., motor vehicle crashes), but

they also may have suffered milder injuries. The generalizability of sports concussion to the larger population of patients with mTBI remains an open question.

To overcome some of the aforementioned weaknesses of acute studies in mTBI, we have used a standard, widely accepted definition of mTBI in a prospective design with a series of unselected patients recruited from hospital EDs with mild TBI or orthopedic injuries (OIs), and healthy uninjured controls. We hypothesized the following: (1) that the severity of emotional and post-concussion symptoms in patients with mTBI will be significantly higher than comparison groups, and deficits will be found in the specific neuropsychological domains of memory, processing speed, and executive functions when assessed within 96 h post-injury, and (2) significant between-group differences would be found more often or more robustly in contrasts of mTBI and typically developing control (TDC) performance than between the mTBI and OI comparison group.

Methods

Data for this study were obtained as part of a larger translational study of parallel assessment between human mTBI and traumatic axonal injury involving a head rotational acceleration technique in a porcine model of mTBI. Given the requirements of the animal study, the corresponding age range in humans was set at 12–30 years.

Participants

A total of 209 participants were recruited for this study. Of this sample, 15 participants were excluded because they were recruited and/or assessed >96 h post-injury, 2 were enrolled in the ED and allowed to go home but failed to return for the baseline assessment, 6 were excluded for meeting exclusion criteria after enrollment, and 1 TDC was excluded for a magnetic resonance imaging (MRI)-identified brain abnormality that may have affected neuropsychological performance. A total of three participants in the OI group and one from the TDC group were excluded because of outlier values ($\geq 95\%$ ile) on the Rivermead Post Concussion Symptom Questionnaire (RPCSQ). Another 3 participants were excluded because they failed one or both symptom validity questions (with self-reported ratings of moderate or severe problems after their injury) that the primary author added to the RPCSQ from the Everyday Memory Questionnaire²⁷ (e.g., “Failing to recognize, by sight, close relatives or friends you meet regularly?” and/or “Forgetting important details about yourself such as your birth date or where you live?”) that would be expected only in patients with severe TBI or moderate to severe dementia. This resulted in a sample of 73 participants with mTBI, 65 with OI, and 40 TDC (total sample $n = 178$).

A consecutive series of patients were prospectively recruited in the Houston area’s three Level-I trauma centers (which include pediatric, county, and private hospitals). Inclusion criteria included patients aged 12–30 years with fluency in either English or Spanish who presented, were treated, and released from the ED less than 24 h after injury. Specific inclusion criteria for patients with mTBI included a documented or witnessed head injury, GCS²⁸ score of 13–15, loss of consciousness <30 minutes, post-traumatic amnesia (PTA) <24 h, and no trauma-related abnormalities on computed tomography (CT) scan. Patients were assessed with the Galveston Orientation and Amnesia Test (GOAT)²⁹ to determine whether they were in PTA defined as a GOAT score ≤ 75 at the time of informed consent. No patient was determined to be in PTA at the time of study enrollment.

The definition of mTBI used in this study followed the guidelines of the American Congress of Rehabilitation Medicine.³⁰ Inclusion criteria for patients with OI included injury to extremities or

pelvis with an Abbreviated Injury Scale (AIS)³¹ score of <3 in any defined body region, and no evidence of head injury. Patients in both groups were excluded for the following: previous head injury necessitating hospitalization (including treatment and discharge from ED), AIS ≥ 3 for any body part, significant history of pre-existing mental disorders (e.g., psychotic disorder, bipolar disorder, and pre-injury post-traumatic stress disorder [PTSD] diagnosed by psychiatrist/psychologist), Alcohol Use Disorders Identification Test (AUDIT)^{32,33} score ≥ 8 , Drug Abuse Screening Test (DAST-10)^{34–36} score ≥ 2 , blood alcohol level >80 mg/dL (or ED documentation of clinical intoxication) at the time of informed consent, left-hand dominant, presence of contraindications for MRI (e.g., shrapnel, ferrous metal implants, pacemaker, claustrophobia, etc.), or positive pregnancy test.

Participants were also excluded if they were not fluent in either English or Spanish. TDCs who had no history of mental disorder, formally diagnosed Attention Deficit Hyperactivity Disorder (ADHD), learning disabilities (LD), PTSD (diagnosed by psychologist or psychiatrist), OI necessitating medical treatment (e.g., private physician, urgent care clinic, ED visit, or hospitalization), or head injury were recruited to match those in the mTBI group for sex, ethnicity, years of education, and age (± 1 year). Every attempt was also made to equate the groups for overall socioeconomic status.

Moderator variables

Visual Analog Scales (VAS pain and fatigue). Participants were asked to place a mark on a 100-mm line with anchor points at 0 – “no pain at all” and 100 – “worst pain in your whole life” to rate their current level of pain. The distance from the 0 anchor point to their mark was measured (in mm) and used as an index of pain severity. The same technique also was used to gauge their current level of fatigue with the anchor points of 0 – “not tired at all” and 100 – “very tired.”

Perceived Stress Scale (PSS). The PSS is a widely used psychological instrument for measuring the degree to which current situations in one’s life are perceived as stressful. Items specifically assessed how unpredictable, uncontrollable, and overloaded participants regarded themselves in the previous month. The total score was used as the primary variable.

Emotional and post-concussion measures

RPCSQ. The RPCSQ^{37–39} is a 16-item self-report of cognitive, emotional, and somatic complaints that are commonly reported after mTBI. Factor analyses have elicited a three-factor solution comprising cognitive, somatic, and emotional problems,³⁹ although variations have been reported.⁴⁰ The participants were asked to rate the severity of each symptom (currently compared with pre-injury levels) from 0 – “not experienced at all” to 4 – “severe problem.” The total score was used as the primary variable in this study.

PTSD Checklist – Civilian Form (PCL-C). The PCL-C^{41,42} is the civilian version of a 17-item self-report measure of PTSD symptom severity comprising required symptoms from the *Diagnostic and Statistical Manual of Mental Disorders-IV*.⁴³ Participants were asked to rate how much they have been bothered by each of the symptoms (5-point Likert scale from 1 – “not at all” to 5 – “extremely”) since their injury. Higher scores indicate greater symptom severity. The total score was used as the primary variable in this study.

Brief Symptom Inventory (BSI). The BSI⁴⁴ is a 53-item, self-report measure of psychological distress. Participants were asked to rate how much they have been bothered by each of the

symptoms (5-point Likert scale from 1 – “not at all” to 5 – “extremely”) since their injury. Higher scores indicate greater psychological distress. The Global Severity Index (GSI) raw score was used as the primary variable in this study.

Neuropsychological measures

Verbal Selective Reminding Test (VSRT). The VSRT^{45,46} is a measure of verbal episodic memory. In this study, the six-trial version was used in which the examiner presents 12 semantically unrelated words on the first trial followed by selective presentation of only those words that the participant failed to recall on each preceding trial. A delayed free recall trial is given 30 minutes after the sixth (or last) learning trial. The two primary variables in this study are (1) consistent long-term retrieval (CLTR; the total number of words recalled calculated for each word beginning with the first trial after which it was recalled consistently through trial six) and (2) delayed recall (the total number of words recalled after 30-minute delay).

BVMT-R. The BVMT-R⁴⁷ is a measure of visuospatial learning and memory. Participants are shown design stimuli in a 2×3 array for 10 sec and asked to draw as many of the figures as they can in the correct location. This procedure is used for three learning trials. The participants are again asked to draw these figures following a 25-minute delay. Total points accrued across the learning trials and the score for delayed recall are the primary variables in this study.

SDMT. The SDMT⁴⁸ is a timed substitution task that has demonstrated high sensitivity in detecting processing speed deficits because of cerebral dysfunction. Using a reference key, the participant is asked to pair numbers associated with simple geometric figures within a fixed time limit. In the written format, the participant writes the correct number below each geometric figure. In the oral format that follows, the participant verbally produces the correct number associated with each figure and the examiner records these responses. The total numbers of correct responses for written and oral versions are the primary variables.

Delis-Kaplan Executive Functioning System Color-Word Interference Test (D-KEFS CWIT). The CWIT⁴⁹ assesses inhibitory processes by contrasting performance latencies for (1) naming blocks of color, (2) reading color words (i.e., “red,” “blue”) presented in black ink, and (3) naming the color of words printed in dissonant-colored ink (inhibition condition, e.g., the word “blue” printed in red ink). This inhibition of a pre-potent response has also been called the Stroop effect.⁵⁰ In the D-KEFS version of this task, an additional condition (Inhibition-Switching) has been included in which the participant is asked to switch between naming the ink color of dissonant-colored words and reading the words themselves (stimuli demarcated with a rectangular box enclosing the word). The raw score for the Inhibition and Inhibition-Switching conditions are the primary variables.

Delis-Kaplan Executive Functioning System Verbal Fluency Test (D-KEFS VFT). The D-KEFS VFT⁴⁹ includes three conditions: (1) Letter Fluency, (2) Category Fluency, and (3) Category-Switching. Two of the D-KEFS VFT conditions (i.e., Letter Fluency and Category Switching) have demonstrated at least modest criterion validity in TBI assessment.⁵¹ For Letter Fluency, the participant was asked to generate as many words as possible conforming to first-letter cues and other specific rules (avoiding production of words that are numbers, proper names, or the same words with different suffixes) in three, 60-sec trials. In Category Fluency, the participant is given a category cue and asked to generate as many words in that category as they can in two, 60-sec

trials. For the Category-Switching condition, the participant is asked to generate as many words as they can alternating between two different category cues (different from those in the Category Fluency condition) in one, 60-sec trial. The primary variables in this study are the raw scores for (1) Letter Fluency, (2) Category Fluency, and (3) Category-Switching.

Procedure

An unselected series of participants were prospectively screened and recruited from the EDs at the three American College of Surgeons Level-I trauma centers (Memorial Hermann Hospital-Texas Medical Center, Ben Taub General Hospital, and Texas Children’s Hospital) in Houston, TX, by study personnel according to a rotating schedule representing all shifts and days of the week. The diagnosis of TBI was made by ED trauma physicians, and GCS²⁸ ratings were made by ED trauma physicians and/or medical staff. AIS³¹ ratings were made by AIS-certified research nurses based on detailed medical record review, which were used to calculate the Injury Severity Score (ISS). All head CT scans were read and coded by a board-certified neuroradiologist (JVH). Although every attempt was made to screen and enroll the patients while in the ED, patients were allowed to go home from the ED and return for the baseline assessment; the target window for this assessment was <96 h post-injury.

Data analysis

Statistical significance was defined as $\alpha=0.05$ for all analyses unless otherwise specified. Planned comparisons were analyzed holding significance at $\alpha=0.05$, and all *post-hoc* comparisons were adjusted using the Bonferroni correction for multiple comparisons. All analyses were conducted with SAS software for Windows, Version 9.3. Previous studies have found that emotional and post-concussion symptoms vary with age and sex. In addition, many neuropsychological measures are sensitive to age and sex effects. For these reasons, these specific demographic variables and their interactions with group were included in the analyses. Because age and sex were variables included as interaction terms, all analyses were performed on raw scores.

Results

Sample characteristics

A total of 178 participants (mTBI=73, OI=65, and TDC=40) were enrolled in the study and met inclusion/exclusion criteria (Table 1). The groups were not significantly different in terms of reported pre-injury levels of reported alcohol use ($p=0.54$) or drug use ($p=0.71$). Regarding demographic factors, the groups did not differ for age at injury ($p=0.32$), sex distribution ($p=0.38$), years of education ($p=0.45$), socioeconomic status (Socioeconomic Composite Index [SCI]; $p=0.12$), or occupational status ($p=0.97$). The mTBI and OI groups did not differ in time post-injury ($p=0.45$) at the baseline assessment. As expected, the groups differed significantly by mechanism of injury in that the mTBI group was more frequently involved in motor vehicle crashes, and the OI group more often sustained relatively lower-velocity injuries (e.g., sports-related injuries, falls/jumps). The groups also differed for overall injury severity, which was expected because the head region was not excluded from the total ISS,³¹ which increased the ISS for the mTBI group because of coding for concussion; however, when the ISS was modified to exclude the head region (M-ISS), the OI group had significantly greater extracranial injury severity.

Effects of secondary gain and concomitant suboptimal effort are well recognized (if infrequently accounted for) in the mTBI

TABLE 1. DEMOGRAPHIC VARIABLES OF THE SAMPLE

Variable	mTBI (n=7)	OI (n=65)	TDC (n=40)	Statistical comparison
Age at injury (years), mean (SD)	19.1 (5.0)	19.9 (5.7)	20.6 (5.2)	$F(2, 175)=1.16, p=0.32$
Sex (female:male)	20:53	20:45	16:24	$\chi^2(2)=1.92, p=0.38$
SCI, mean (SD)	-0.18 (0.96)	0.02 (0.94)	0.21 (1.08)	$F(2, 175)=2.17, p=0.12$
Education (years), mean (SD)	10.5 (2.7)	10.8 (2.9)	11.3 (3.2)	$F(2, 175)=0.80, p=.045$
History of ADHD, <i>n</i> (% yes)	5 (6.9)	6 (9.2)	0 (0)	$p=0.15^*$
History of LD, <i>n</i> (% yes)	2 (2.7)	1 (1.5)	0 (0)	$p=0.80^*$
Race, <i>n</i> (%)				
European American	44 (60.3)	39 (60.0)	25 (62.5)	$p=0.95^*$
African American	27 (37.0)	23 (35.4)	13 (32.5)	
Asian	0 (0)	1 (1.5)	1 (2.5)	
Bi- or multiracial	2 (2.7)	2 (3.0)	1 (2.5)	
Ethnicity, <i>n</i> (%)				
Hispanic	26 (35.6)	28 (43.1)	13 (32.5)	$\chi^2(2)=1.39, p=0.49$
Non-Hispanic	47 (64.4)	37 (56.9)	27 (68.5)	
Primary language, <i>n</i> (%)				
English	70 (95.9)	65 (100)	40 (100)	$p=0.24^*$
Spanish	3 (4.1)	0 (0)	0 (0)	
Occupation, <i>n</i> (%)				
Professional/technical	3 (4.1)	3 (4.6)	2 (5.0)	$p=0.97^*$
Managers, clerical, sales	6 (8.2)	7 (10.8)	4 (10.0)	
Skilled worker	3 (4.1)	0 (0)	1 (2.5)	
Students, unemployed	49 (67.1)	44 (67.7)	25 (62.5)	
Semi-skilled worker	8 (11.0)	7 (10.7)	6 (15.0)	
Unskilled worker	4 (5.5)	4 (6.2)	2 (5.0)	
VAS fatigue	31.0 (30.2)	22.7 (26.6)	21.0 (26.3)	$F(2,174)=2.22, p=0.11$
VAS pain	24.8 (25.6)	23.0 (21.1)	3.8 (7.8)	$F(2,174)=14.34, p<0.0001$
PSS	16.8 (6.7)	13.3 (5.5)	12.4 (6.1)	$F(2,175)=8.89, p=0.0002$
AUDIT, mean (SD)	3.1 (3.9)	2.4 (3.0)	3.0 (3.4)	$F(2,168)=0.63, p=0.54$
DAST-10, mean (SD)	1.0 (1.6)	0.8 (1.4)	0.9 (1.3)	$F(2,175)=0.34, p=0.71$

*Fisher exact test.

mTBI, mild traumatic brain injury; OI, orthopedic injury; TDC, typically developing control; SD, standard deviation; SCI, Socioeconomic Composite Index; ADHD, attention deficit hyperactivity disorder; LD, learning disabilities; VAS fatigue, Visual Analog Fatigue Scale; VAS pain, Visual Analog Pain Scale; PSS, Perceived Stress Scale; AUDIT, Alcohol Use Disorders Identification Test; DAST-10, Drug Abuse Screening Test, 10-item version.

literature.^{38,52–59} Using the methodology reported by McCauley and colleagues,⁵³ participants were queried regarding current involvement in, or anticipation of future, injury-related litigation or receipt of compensation. Of the mTBI group, 9.0% reported involvement in or planning of litigation compared with 6.3% of the OI group, which was not significantly different (Fisher exact test, $p=0.75$), and 4.4% of the mTBI group reported receiving some form of injury-related compensation compared with 4.7% of the OI group, which was not significantly different (Fisher exact test, $p=1.0$).

Moderator variables

Measures of fatigue, perceived stress, and pain were explored as possible moderator variables or covariates. The overall F-test for fatigue was not significant ($F[2,174]=2.22, p=0.11$), but the F-test for pain was significant ($F[2,174]=14.3, p<0.0001$). The F-test for perceived stress was significant ($F[2,175]=8.89, p=0.0002$); in *post-hoc* comparisons, the stress level reported by the mTBI was significantly higher compared with the OI ($p=0.0008$) and TDC groups ($p=0.0003$), and the OI and TDC groups did not differ ($p=0.49$). Finally, in *post-hoc* comparisons, pain severity was similar between the mTBI and OI groups ($p=0.64$), and both groups reported significantly higher pain than the TDC ($p<0.0001$ for both comparisons).

The effect of analgesics on pain severity within the mTBI and OI groups was investigated in a Group $\times$ Pain Medication (present vs. absent) analysis of variance. The Group $\times$ Pain Medication interaction was not significant ($p=0.93$). Main effects were then explored and the effect of group was not significant ($p=0.63$), but the effect of medication was associated with significantly higher reported VAS Pain levels (analgesic $M=37.6 \pm 3.6$, no-analgesic $M=23.3 \pm 2.8$; $F[2,90]=9.84, p=0.0023$). Those with injuries and pain significant enough to necessitate analgesics reported greater pain severity than those not needing analgesics, and the overall pain level was not significantly different between the mTBI and OI groups. Given between-group differences for these moderators variables, the pain and perceived stress variables were explored as covariates (as appropriate to the dependent variable of interest) of emotional and neuropsychological variables.

Emotional and post-concussion variables

Separate analyses of covariance (ANCOVA) were conducted for each of the three emotional variables including the three-way interaction of age, sex, and group. The VAS Pain variable was included as a covariate. Perceived stress was not explored as a covariate with the emotional and post-concussion variables because stress is a component of all three dependent measures. Pain was not found to have significant effect on the dependent variables

TABLE 2. INJURY-RELATED VARIABLES OF THE SAMPLE

Variable	mTBI (n = 73)	OI (n = 65)	Statistical comparison
Time post-injury (h)	60.5 (21.5)	63.3 (22.9)	F(1,136) = 0.57, $p = 0.45$
GCS (lowest)	14.8 (0.5)	15.0 (0)	N/A
GOAT	92.9 (7.9)	97.1 (12.8)	F(1,134) = 5.51, $p = 0.02$
ISS	2.0 (1.9)	1.4 (1.1)	F(1,132) = 6.23, $p < 0.02$
M-ISS	0.61 (1.3)	1.3 (1.0)	F(1,132) = 12.5, $p = 0.0006$
Litigation, n (%) yes)	6 (9.0)	4 (6.3)	$p = 0.74^*$
Compensation, n (%) yes)	3 (4.4)	3 (4.7)	$p = 1.0^*$
Mechanism of injury, n (%)			
MVA/MCA/RV	31 (42.4)	6 (9.2)	
Struck by motor vehicle	4 (5.5)	1 (1.5)	
Assault/fight	8 (11.0)	6 (9.2)	
Hit by falling object	3 (4.1)	5 (7.7)	$p < 0.0001^*$
Fall/jump	14 (17.8)	19 (29.3)	
Sports/play	14 (19.2)	26 (40.0)	
Other	0 (0)	2 (3.1)	
Duration of LOC, n (%)			
None	5 (6.9)	N/A	
None, but dazed (AMS)	11 (15.0)	N/A	
< 1 min	14 (19.2)	N/A	
1–5 min	24 (32.9)	N/A	
6–10 min.	2 (2.7)	N/A	N/A
11–20 min.	4 (5.4)	N/A	
21–30 min.	8 (11.0)	N/A	
Unknown	5 (6.9)	N/A	

*Fisher exact test.

mTBI, mild traumatic brain injury; OI, orthopedic injury; GCS, Glasgow Coma Scale; GOAT, Galveston Orientation and Amnesia Test; ISS, Injury Severity Score; M-ISS, Modified Injury Severity Score (ISS not including head region); MVA, motor vehicle accident; MCA, motorcycle accident; RV, recreational or other off-road vehicle; LOC, loss of consciousness; AMS, altered mental status.

and was therefore removed from all succeeding models. The three-way interaction of Age $\times$ Gender $\times$ Group was not significant for any dependent variable, and models including the two-way interactions of Age $\times$ Group, Gender $\times$ Group, and Age $\times$ Gender were then reviewed.

BSI. The GSI from the BSI was the main variable of interest. None of the two-way interactions were significant, so main effects were explored next. Age and sex were not significant ($p = 0.08$ and $p = 0.21$, respectively), but the effect of group was significant ($F[2,169] = 19.76$, $p < 0.0001$). *Post-hoc* comparisons indicated that emotional distress was higher in the mTBI group vs. OI, and mTBI vs. TDC (both $p < 0.0001$), but no significant difference was found between OI vs. TDC (Table 3).

RPCSQ. Only the Age $\times$ Group interaction was significant ($F[2,168] = 4.86$, $p < 0.009$). To decompose the Age $\times$ Group in-

teraction, RPCSQ scores were plotted against age (mean age of the full sample ± 1 standard deviation), which revealed that higher RPCSQ scores were associated with increasing age (Fig. 1A); RPCSQ scores were flat across the age range for the OI and TDC groups, but increased as age increased in the mTBI group. Follow-up analyses found that the quadratic effect of age was not significant.

Subscales of the RPCSQ (i.e., cognitive, somatic, and emotional) were analyzed including the two-way interactions of Age $\times$ Group, Gender $\times$ Group, and Age $\times$ Gender. For the Cognitive subscale, Age $\times$ Gender and Gender $\times$ Group interactions were not significant, but the Age $\times$ Group interaction was ($F[2,167] = 4.38$, $p = 0.01$). This interaction was decomposed as in the RPCSQ total score above; report of increasing cognitive complaints with increasing age was found only within the mTBI group. There was a main effect of gender ($F[1,167] = 4.26$, $p = 0.04$) such that females reported greater severity of cognitive problems (Fig. 1B).

TABLE 3. EMOTIONAL AND POSTCONCUSSION VARIABLES

Measure	mTBI L-S mean (SE)	OI L-S mean (SE)	TDC L-S mean (SE)	Post-hoc comparisons		
				mTBI vs. OI	mTBI vs. TDC	OI vs. TDC
BSI	0.89 (0.06)	0.44 (0.06)	0.36 (0.08)	$p < 0.0001$	$p < 0.0001$	$p = 0.43$
RPCSQ	16.4 (0.94)	3.6 (0.99)	2.0 (1.3)	$p < 0.0001$	$p < 0.0001$	$p = 0.32$
PCL-C	32.1 (1.2)	22.6 (1.2)	23.1 (1.6)	$p < 0.0001$	$p < 0.0001$	$p = 0.84$

Scores shown are least-squares means after adjustment for age, gender, and any significant interactions.

mTBI, mild traumatic brain injury; L-S means, least squares means; SE, standard error; OI, orthopedic injury; TDC, typically developing control; BSI, Global Severity Index from the Brief Symptom Inventory; RPCSQ, Rivermead Post Concussion Symptom Questionnaire; PCL-C, PTSD-Checklist, Civilian form.

FIG. 1. (A) Rivermead Total Score Age × Group Interaction. L-S, least squares; mTBI, mild traumatic brain injury; OI, orthopedic injury; TDC, typically developing control. (B) Rivermead Cognitive Subscale Score Age × Group Interaction. RPCSQ, Rivermead Post Concussion Symptom Questionnaire; L-S, least squares; mTBI, mild traumatic brain injury; OI, orthopedic injury; TDC, typically developing control. (C) Rivermead Somatic Subscale Score Age × Group Interaction. RPCSQ, Rivermead Post Concussion Symptom Questionnaire; L-S, least squares; mTBI, mild traumatic brain injury; OI, orthopedic injury; TDC, typically developing control.

Similarly for the Somatic subscale, only the Age × Group interaction was significant ($F[2,168] = 3.77, p = 0.025$). Decomposition of the interaction indicated that somatic complaints increased with increasing age only within the mTBI group. There was a main effect of sex ($F[1,167] = 7.72, p = 0.006$) such that females reported greater severity of somatic complaints (Fig. 1C). Finally, analyses of the Emotional subscale revealed no significant two-way interactions, so main effects were explored next. There was no effect of sex ($p = 0.10$), but there were main effects for group ($F[2,168] = 11.83, p < 0.0001$; emotional complaints were significantly higher in the mTBI group compared with both OI and TDC) and age ($F[1,168] = 8.38, p = 0.0043$) such that increasing age was associated with increasing severity of emotional symptoms.

PTSD- PCL-C. The Age × Gender interaction was not significant and was removed from the model. The Age × Group ($F[2,168] = 7.05, p = 0.001$) and Gender × Group ($F[2,164] = 4.14, p < 0.02$) interactions were significant. To decompose the Age × Group interaction, PCL-C scores were plotted against age (mean age of the full sample ± 1 standard deviation). As can be seen in Figure 2, PCL-C scores were essentially flat across the age range for the OI and TDC groups, but increased with increasing age in the mTBI group. Follow-up analyses determined that there was no significant quadratic effect of age. In decomposing the Gender × Group interaction, Figure 3 shows that PCL-C scores were similar in both males and females in the OI and TDC groups; within the mTBI group, PCL-C scores were significantly elevated, but females reported greater symptom severity than males.

Neuropsychological variables

Similar to the procedure for the emotional and post-concussion variables, separate ANCOVAs were conducted for each of the neuropsychological variables of interest including the three-way interaction of age, sex, and group. Pain and perceived stress variables were included as covariates; VAS Fatigue was not included because no group-level differences were found. Pain was not found to have a significant effect on any neuropsychological variable and was removed from all subsequent analyses. Finally, perceived stress had a significant effect only on the SDMT-Oral and D-KEFS

FIG. 2. PTSD Checklist – Civilian Form (PCL-C) Age × Group Interaction. L-S, least squares; mTBI, mild traumatic brain injury; OI, orthopedic injury; TDC, typically developing control.

FIG. 3. PTSD Checklist – Civilian Form (PCL-C) Gender $\times$ Group Interaction. L-S, least squares; mTBI, mild traumatic brain injury; OI, orthopedic injury; TDC, typically developing control.

Inhibition-Switching variables and was retained for these models only. The three-way interaction of Age $\times$ Gender $\times$ Group was not significant for any dependent variable, and models including the two-way interactions of Age $\times$ Group, Gender $\times$ Group, and Age $\times$ Gender were reviewed next.

Memory. In analyses of the VSRT, CLTR was analyzed first. The Age $\times$ Gender and the Age $\times$ Group interactions were not significant and were removed from the model. The Gender $\times$ Group interaction was significant ($F[2,169]=4.79, p<0.01$), but the effect of age was not significant ($p=0.96$). As illustrated in Figure 4, females with mTBI performed poorly compared with females in the OI and TDC groups. For males, performance was lower in the mTBI and OI groups compared with the TDC group. Delayed free recall was analyzed next. Similar to the CLTR results, the Age $\times$ Gender and the Age $\times$ Group interactions were not significant and were removed from the model. The Gender $\times$ Group interaction was significant ($F[2,168]=3.21, p<0.05$), and the main effect of age again was not significant ($p=0.16$).

Figure 5 demonstrates a greater disparity between females with mTBI compared with females in the OI and TDC groups, whereas

FIG. 4. Verbal Selective Reminding Test (consistent long-term retrieval) (VSRT [CLTR]) Gender $\times$ Group Interaction.

FIG. 5. Verbal Selective Reminding Test (VSRT) (Delayed Recall) Group $\times$ Gender Interaction. L-S, least squares; mTBI, mild traumatic brain injury; OI, orthopedic injury; TDC, typically developing control.

the differences between groups for males were less robust. In *post-hoc* comparisons (Table 4), note that the mTBI group performed significantly poorer than the OI and TDC groups, but that the OI and TDC group performance was similar.

There were no significant two-way interactions for BVMT-R learning or delayed recall. Main effects for BVMT-R learning included age ($F[1,165]=7.83, p<0.006$) and a trend for group ($F[2,165]=2.74, p=0.07$); sex was not significant ($p=0.77$). Main effects for BVMT-R delayed recall included age ($F[1,165]=8.59, p<0.004$) and a trend for group ($F[2,165]=2.7, p=0.07$); sex was not significant ($p=0.88$). For both BVMT-R dependent variables, older age was associated with lower scores. *Post-hoc* comparisons on the BVMT-R indicated that the mTBI group performed significantly poorer compared with the TDC, but only a trend was found for comparisons with the OI group; the OI and TDC performances were comparable.

Processing speed. The written administration of SDMT was analyzed first. Only the Age $\times$ Group interaction was significant ($F[2,165]=2.97, p=0.05$), but there was no main effect of sex ($p=0.96$). Interaction decomposition was performed as before, which revealed that lower SDMT Written scores were associated with increasing age in the mTBI group (Figure 6); SDMT Written scores were relatively flat across the age range for the OI and TDC groups, but were inversely related in the mTBI group. Follow-up analyses found that the quadratic effect of age was not significant.

For the SDMT oral administration, there was a trend for the effect of perceived stress ($F[1,169]=3.27, p=0.07$) and no significant two-way interactions. The group effect was significant ($F[2,169]=10.18, p<0.0001$), but there was no effect of age ($p=0.78$) or sex ($p=0.89$). In *post-hoc* comparisons for SDMT-Written, the mTBI group performed similarly to the OI group, but significantly poorer than the TDC group; however, the OI group performed significantly poorer than the TDC group. The mTBI group performed significantly poorer than the OI and TDC groups on SDMT-Oral, but the OI group performed similarly to the TDC.

Executive function. The two D-KEFS CWIT variables were analyzed first, and there were no significant two-way interactions.

TABLE 4. NEUROPSYCHOLOGICAL VARIABLES

Measure	<i>mTBI</i> L-S mean (SE)	<i>OI</i> L-S mean (SE)	<i>TDC</i> L-S mean (SE)	Post-hoc comparisons		
				<i>mTBI</i> vs. <i>OI</i>	<i>mTBI</i> vs. <i>TDC</i>	<i>OI</i> vs. <i>TDC</i>
VSRT (CLTR)	30.1 (2.1)	41.6 (2.1)	43.7 (2.5)	$p=0.0002$	$p<0.0001$	$p=0.52$
VSRT (Delayed Free Recall)	8.1 (0.3)	9.8 (0.31)	9.8 (0.37)	$p=0.0003$	$p=0.0005$	$p=0.87$
BVMT-R (Learning)	22.5 (0.67)	23.8 (0.7)	24.9 (0.84)	$p=0.14$	$p<0.03$	$p=0.34$
BVMT-R (Delayed Free Recall)	8.3 (0.24)	8.9 (0.25)	9.1 (0.3)	$p=0.08$	$p<0.04$	$p=0.58$
SDMT-Written	45.7 (1.2)	49.2 (1.2)	53.3 (1.5)	$p=0.03$	$p=0.0001$	$p<0.04$
SDMT-Oral	52.1 (1.6)	59.4 (1.6)	63.1 (2.0)	$p=0.001$	$p<0.0001$	$p=0.14$
D-KEFS CWIT Inhibition	55.3 (1.8)	54.9 (1.8)	54.3 (2.2)	$p=0.86$	$p=0.72$	$p=0.84$
D-KEFS CWIT Inhibition-Switching	66.6 (2.4)	67.4 (2.4)	65.9 (3.0)	$p=0.81$	$p=0.85$	$p=0.68$
D-KEFS VFT Letter Fluency	32.5 (1.3)	32.8 (1.3)	37.7 (1.6)	$p=0.86$	$p<0.02$	$p<0.02$
D-KEFS VFT Category Fluency	36.0 (1.2)	37.2 (1.2)	38.6 (1.5)	$p=0.47$	$p=0.18$	$p=0.48$
D-KEFS VFT Category Switching	11.7 (0.39)	12.3 (0.39)	13.1 (0.49)	$p=0.29$	$p<0.04$	$p=0.21$

Scores shown are least-squares means after adjustment for age, sex, and (as appropriate) for perceived stress and any significant interactions.

mTBI, mild traumatic brain injury; L-S, least squares; SE, standard error; OI, orthopedic injury; TDC, typically developing control, SRT = Verbal Selective Reminding Test; CLTR, consistent long-term retrieval; BVMT-R, Brief Visualspatial Learning Test-Revised; SDMT, Symbol-Digit Modalities Test; D-KEFS, Delis-Kaplan Executive Function System; CWIT, Color-Word Interference Test; VFT, Verbal Fluency Test;

L-S Means, least squares means; SE, standard error.

In the Inhibition condition, there was no effect of age ($p=0.10$), sex ($p=0.58$), or group ($p=0.94$). For Inhibition-Switching, there also were no effects of age ($p=0.63$), sex ($p=0.41$), or group ($p=0.92$), but perceived stress was significant ($F[1,165]=5.58$, $p<0.02$) such that higher stress was associated with better performance. Three dependent measures were analyzed from the D-KEFS VFT: Letter Fluency, Category Fluency, and Category-Switching. There were no significant two-way interactions for any of the dependent variables. Main effects for Letter Fluency included group ($F[2,166]=3.68$, $p<0.03$) and age ($F[1,166]=15.21$, $p=0.0001$), but no effect of sex ($p=0.94$). Main effects for Category Fluency included age ($F[1,166]=18.91$, $p<0.0001$), but no significant effect of sex ($p=0.27$) or group ($p=0.40$). Results for Category-Switching were not significant for group ($p=0.10$), but were significant for age ($F[1,166]=21.68$, $p<0.0001$), and sex ($F[1,166]=4.0$, $p<0.05$) such that higher scores were associated with female sex. For D-KEFS VFT, the mTBI group performed poorer than the TDC, but not the

OI, on Letter Fluency; the OI group performed poorer than the TDC. For Category Fluency, there were no group differences between the mTBI, OI, and TDC. For Category-Switching, the mTBI group performed similarly to the OI, but significantly poorer than the TDC; the OI group performed similarly to the TDC.

Discussion

Partial support was found for our first hypothesis; emotional and PCS symptoms were significantly elevated in the mTBI group when compared with either the OI or TDC groups, which is consonant with other reports of PCS symptoms in the literature when patients were assessed in the first week post-injury^{8,9,12,14,15} and after sports-related concussions.^{22–24,26,60,61} In terms of neuropsychological performance, the mTBI group demonstrated decreased verbal learning and recall (VSRT), and slowed processing speed (SDMT) compared with OI, but did not differ on other commonly used measures sensitive to mTBI including response inhibition (Stroop) or letter fluency. Findings for slowed processing speed and memory are consistent with previous research of acute impairments after non-sport mTBI^{9,12,14–17} and sports-related concussions.^{19–23,25,26,60–62} Impairments in episodic memory and processing speed have been reported in prospective studies that used eligibility criteria similar to the present study, including GCS 13–15 and normal CT scans when available.¹⁵ Our findings confirm these as among the most important cognitive domains to assess after injury from a clinical perspective.

Additional study is necessary to determine an optimal post-injury assessment interval for detection of performance decrements that may be associated with increased risk for persistent difficulties at a later end point or which may relate to return to play decisions in sports-related concussion. Additional study is also needed to establish the relation between these cognitive domains and changes that may be apparent on advanced forms of neuroimaging, symptom report, and aspects of specialized physical examination (e.g., vestibular system, eye movements, etc.).

Support also was found for our second hypothesis—namely, that significant between-group differences would be more prevalent or robust when comparing the mTBI and TDC groups than mTBI and OI groups. As illustrated in Table 4, significant differences were

FIG. 6. Symbol-Digit Modalities Test (Written Administration) (SDMT) Age $\times$ Group Interaction. L-S, least squares; mTBI, mild traumatic brain injury; OI, orthopedic injury; TDC, typically developing control.

found between mTBI and OI groups for 4 of 11 variables whereas 8 of 11 significant differences were found between the mTBI and TDC groups. Even if a Bonferroni correction was used to determine significance within each family of comparisons ($p < 0.005$), 2 of 11 variables survived as significantly different in mTBI versus OI whereas 4 of 11 differences were significant in mTBI versus TDC comparisons. Measures of verbal memory (CLTR and delayed free recall) and processing speed (SDMT written and oral modalities) revealed significant differences using either comparison group. The SDMT written modality and D-KEFS Letter Fluency measures revealed significant differences between the OI and TDC groups.

These results also highlight the importance of appropriate comparison group selection. While vigorous discussions continue as to whether or not orthopedically injured controls should be used as the optimal comparison group for patients with mTBI, it is clear that when relevant demographic factors are controlled, typically developing participants offer an attractive comparison alternative. Multiple comparisons notwithstanding, the TDC group outperformed the OI in terms of commonly used measures of processing speed and time-based executive functioning. A plausible explanation for this difference is the presence of occult mTBI. While this cannot be ruled out with absolute certainty, we used rigorous screening and adherence to inclusion and exclusion criteria, which should have significantly reduced this possibility.

As a secondary explanation given the number of sports-related injuries reported (40% in the OI group; Table 2), the possibility arises that previous single or multiple sub-concussive blows or concussions may have gone unreported and thus attenuated the mTBI versus OI neuropsychological performance differences. Again, this cannot be ruled out with complete certainty, but our procedures minimized this to the extent reasonably achievable. On the whole, it appears that uninjured, typically developing persons should not be ruled out as a viable, if not more appropriate, comparison group with those with mTBI.

Overall, our results appear to be consistent with previous reports of traumatic axonal injury (TAI) associated with mTBI, which generally include deficits in the domains of processing speed, memory, and executive function.⁶³ Advanced forms of neuroimaging are needed for detecting TAI. Clinical correlation of modalities such as diffusion tensor imaging (DTI) with neuropsychological deficits has been successful. For instance, Bazarian and coworkers⁶⁴ found that altered DTI indices acquired within 72 h post-injury correlated significantly with concurrent assessment of visuomotor speed and impulse control in patients with mTBI. More recent work by Messé and associates⁶⁵ reported that patients with poor outcome 3–4 months after mTBI demonstrated reductions in long association white matter tracts (assessed between 7–28 days post-injury) compared with those with good outcome. In addition, Messé and colleagues⁶⁶ reported that patients with mTBI and PCS symptoms demonstrated greater and more widespread loss of white matter integrity that did not resolve over 6 months post-injury as did that of patients with mTBI and PCS symptoms that had resolved. Future research with this cohort of patients will include the analysis of DTI to ascertain whether TAI detected through acute neuroimaging (e.g., <96 h post-injury) is associated with concurrent neuropsychological performance and/or predictive of later outcome.

Limitations

Despite the relatively narrow recruitment window, there remains some variability in the post-injury interval at which each partici-

pant was tested, which could have altered performance; that is, participants assessed earlier may have been more symptomatic than those assessed near the end of the recruitment window. The findings may not generalize to patients with complicated mild injury (i.e., those with GCS of 13–15 and positive neuroimaging findings on emergent brain CT scan). In addition, we acknowledge the limited sensitivity of some of the neuropsychological tests in detecting subtle decrements in some aspects of performance. For example, reaction time was assessed using traditional neuropsychological measures, which are measured via stopwatch at the level of seconds, rather than milliseconds, as is done in computerized measures of reaction time. As is the case in many studies of TBI, our unselected sample included participants with several different injury mechanisms, and the contribution of this factor on outcome warrants further study.

Next, as research personnel conducting the baseline assessments were not blinded to the participant's group status, there is the possibility that this may have introduced some degree of bias and, as such, this is a threat to the internal validity of this study. This threat appears to be minimal because the participant-completed measures do not present significant opportunity for influence from well-trained and experienced examiners, or scoring bias of the neuropsychological measures used in this study because these have demonstrated excellent inter-rater reliability.

Finally, we acknowledge that group-level analyses may not accurately reflect additional sources of person-specific vulnerability to injury and the course of recovery in individual patients or in more specific subgroups on patients with mTBI. Consideration of additional factors, which may be used in the subacute period to identify patients who are at greatest risk for an unusual, delayed, or incomplete course of recovery, is currently under way.

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References

1. National Center for Injury Prevention and Control. 2003. *Report to Congress on Mild Traumatic Brain Injury in the United States: Steps to Prevent a Serious Public Health Problem*. Centers for Disease Control and Prevention: Atlanta.
2. Faul, M., Xu, L., Wald, M.M., and Coronado, V.G. 2010. *Traumatic Brain Injury in the United States: Emergency Department Visits, Hospitalizations and Deaths 2002–2006*. Centers for Disease Control and Prevention, National Center for Injury Prevention and Control. Atlanta.
3. Sosin, D.M., Sniezek, J.E., and Thurman, D.J. (1996). Incidence of mild and moderate brain injury in the United States, 1991. *Brain Inj.* 10, 47–54.
4. Thurman, D.J. (2001). The epidemiology and economics of head trauma, in: *Head Trauma: Basic, Preclinical, and Clinical Directions*. L. Miller, R.L. Hayes, (eds). John Wiley and Sons: New York.

5. Carroll, L.J., Cassidy, J.D., Holm, L., Kraus, J., Coronado, V.G., and WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury. (2004). Methodological issues and research recommendations for mild traumatic brain injury: the WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury. *J. Rehabil. Med. Suppl.* 43, 113–125.
6. Holm, L., Cassidy, J.D., Carroll, L.J., Borg, J.; Neurotrauma Task Force on Mild Traumatic Brain Injury of the WHO Collaborating Centre. (2005). Summary of the WHO Collaborating Centre for Neurotrauma Task Force on Mild Traumatic Brain Injury. *J. Rehabil. Med.* 37, 137–141.
7. Dikmen, S.S., and Levin, H.S. (1993). Methodological issues in the study of mild head injury. *J. Head Trauma Rehabil.* 8, 30–37.
8. McLean, A., Jr., Temkin, N.R., Dikmen, S., and Wyler, A.R. (1983). The behavioral sequelae of head injury. *J. Clin. Neuropsychol.* 5, 361–376.
9. McMillan, T.M., and Glucksman, E.E. (1987). The neuropsychology of moderate head injury. *J. Neurol. Neurosurg. Psychiatry* 50, 393–397.
10. Lidvall, H.F., Linderoth, B., and Norlin, B. (1974). Causes of the post-concussional syndrome. *Acta Neurol. Scand. Suppl.* 56, 3–144.
11. Newcombe, F., Rabbitt, P., and Briggs, M. (1994). Minor head injury: pathophysiological or iatrogenic sequelae? *J. Neurol. Neurosurg. Psychiatry* 57, 709–716.
12. Ponsford, J., Willmott, C., Rothwell, A., Cameron, P., Kelly, A.M., Nelms, R., Curran, C., and Ng, K. (2000). Factors influencing outcome following mild traumatic brain injury in adults. *J. Int. Neuropsychol. Soc.* 6, 568–579.
13. Mild Traumatic Brain Injury Committee American Congress of Rehabilitation Medicine Head Injury Interdisciplinary Special Interest Group. (1993). Definition of mild traumatic brain injury. *J. Head Trauma Rehabil.* 8, 86–87.
14. MacFlynn, G., Montgomery, E.A., Fenton, G.W., and Rutherford, W. (1984). Measurement of reaction time following minor head injury. *J. Neurol. Neurosurg. Psychiatry* 47, 1326–1331.
15. Levin, H.S., Mattis, S., Ruff, R.M., Eisenberg, H.M., Marshall, L.F., Tabaddor, K., High, W.M., Jr., and Frankowski, R.F. (1987). Neuro-behavioral outcome following minor head injury: a three-center study. *J. Neurosurg.* 66, 234–243.
16. Hugenholtz, H., Stuss, D.T., Stethem, L.L., and Richard, M.T. (1988). How long does it take to recover from a mild concussion? *Neurosurgery* 22, 853–858.
17. Brooks, J., Fos, L.A., Greve, K.W., and Hammond, J.S. (1999). Assessment of executive function in patients with mild traumatic brain injury. *J. Trauma* 46, 159–163.
18. Moser, R.S., Schatz, P., Neidzowski, K., and Ott, S.D. (2011). Group versus individual administration affects baseline neurocognitive test performance. *Am. J. Sports Med* 39, 2325–2330.
19. Hinton-Bayre, A.D., Geffen, G., and McFarland, K. (1997). Mild head injury and speed of information processing: a prospective study of professional rugby league players. *J. Clin. Exp. Neuropsychol.* 19, 275–289.
20. Hinton-Bayre, A.D., Geffen, G.M., Geffen, L.B., McFarland, K.A., and Friis, P. (1999). Concussion in contact sports: reliable change indices of impairment and recovery. *J. Clin. Exp. Neuropsychol.* 21, 70–86.
21. McCrea, M., Kelly, J.P., Randolph, C., Kluge, J., Bartolic, E., Finn, G., and Baxter, B. (1998). Standardized assessment of concussion (SAC): on-site mental status evaluation of the athlete. *J. Head Trauma Rehabil.* 13, 27–35.
22. Lovell, M.R., Collins, M.W., Iverson, G.L., Field, M., Maroon, J.C., Cantu, R., Podell, K., Powell, J.W., Belza, M., and Fu, F.H. (2003). Recovery from mild concussion in high school athletes. *J. Neurosurg* 98, 296–301.
23. Lovell, M.R., Collins, M.W., Iverson, G.L., Johnston, K.M., and Bradley, J.P. (2004). Grade 1 or “ding” concussions in high school athletes. *Am. J. Sports Med.* 32, 47–54.
24. Iverson, G.L., Gaetz, M., Lovell, M.R., and Collins, M.W. (2004). Cumulative effects of concussion in amateur athletes. *Brain Inj.* 18, 433–443.
25. Erlange, D., Kaushik, T., Cantu, R., Barth, J.T., Broshek, D.K., Freeman, J.R., and Webbe, F.M. (2003). Symptom-based assessment of the severity of a concussion. *J. Neurosurg.* 98, 477–484.
26. Field, M., Collins, M.W., Lovell, M.R., and Maroon, J. (2003). Does age play a role in recovery from sports-related concussion? A comparison of high school and collegiate athletes. *J. Pediatr.* 142, 546–553.
27. Sunderland, A., Harris, J.E., and Baddeley, A.D. (1983). Do laboratory tests predict everyday memory? A neuropsychological study. *J. Verbal Learning Verbal Behav.* 22, 727–738.
28. Teasdale, G., and Jennett, B. (1974). Assessment of coma and impaired consciousness. A practical scale. *Lancet* 2, 81–84.
29. Levin, H.S., O’Donnell, V.M., and Grossman, R.G. (1979). The Galveston Orientation and Amnesia Test. A practical scale to assess cognition after head injury. *J. Nerv. Ment. Dis.* 167, 675–684.
30. Kay, T. (1993). Mild traumatic brain injury committee of the head injury interdisciplinary special interest group of the American Congress of Rehabilitation Medicine. Definition of mild traumatic brain injury. *J. Head Trauma Rehabil.* 8, 86–87.
31. Committee on Injury Scaling. 1998. *Abbreviated Injury Scale*. Association for the Advancement of Automotive Medicine: Arlington Heights, IL.
32. Bohn, M.J., Babor, T.F., and Kranzler, H.R. (1995). The Alcohol Use Disorders Identification Test (AUDIT): validation of a screening instrument for use in medical settings. *J. Stud. Alcohol* 56, 423–432.
33. Saunders, J.B., Aasland, O.G., Babor, T.F., de la Fuente, J.R., and Grant, M. (1993). Development of the Alcohol Use Disorders Identification Test (AUDIT): WHO Collaborative Project on Early Detection of Persons with Harmful Alcohol Consumption—II. *Addiction* 88, 791–804.
34. Skinner, H.A. (1982). The drug abuse screening test. *Addict. Behav.* 7, 363–371.
35. Bohn, M.J., Babor, T.F., and Kranzler, H.R. 1991. *Validity of the Drug Abuse Screening Test (DAST-10) in Inpatient Substance Abusers*. Department of Health and Human Services. Rockville, MD.
36. Yudko, E., Lozhkina, O., and Fouts, A. (2007). A comprehensive review of the psychometric properties of the Drug Abuse Screening Test. *J. Subst. Abuse Treat.* 32, 189–198.
37. King, N.S., Crawford, S., Wenden, F.J., Moss, N.E., and Wade, D.T. (1995). The Rivermead Post Concussion Symptoms Questionnaire: a measure of symptoms commonly experienced after head injury and its reliability. *J. Neurol.* 242, 587–592.
38. Eyres, S., Carey, A., Gilworth, G., Neumann, V., and Tennant, A. (2005). Construct validity and reliability of the Rivermead Post-Concussion Symptoms Questionnaire. *Clin. Rehabil.* 19, 878–887.
39. Potter, S., Leigh, E., Wade, D., and Fleminger, S. (2006). The Rivermead Post Concussion Symptoms Questionnaire: a confirmatory factor analysis. *J. Neurol.* 253, 1603–1614.
40. Herrmann, N., Rapoport, M.J., Rajaram, R.D., Chan, F., Kiss, A., Ma, A.K., Feinstein, A., McCullagh, S., and Lancot, K.L. (2009). Factor analysis of the Rivermead Post-Concussion Symptoms Questionnaire in mild-to-moderate traumatic brain injury patients. *J. Neuropsychiatry Clin. Neurosci.* 21, 181–188.
41. Blanchard, E.B., Jones-Alexander, J., Buckley, T.C., and Forneris, C.A. (1996). Psychometric properties of the PTSD Checklist (PCL). *Behav. Res. Ther.* 34, 669–673.
42. Weathers, F., Litz, B., Herman, D., Huska, J., and Keane, T. 1993. The PTSD Checklist (PCL): Reliability, Validity, and Diagnostic Utility, in: 9th Annual Convention of the International Society for Traumatic Stress Studies: San Antonio, TX.
43. American Psychiatric Association. 1994. *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. American Psychiatric Association: Washington, D.C.
44. Derogatis L.R. (1993). *Brief Symptom Inventory: Administration, Scoring, and Procedures Manual*. NCS Pearson, Inc.: Minneapolis, MN.
45. Buschke, H. (1973). Selective reminding for analysis of memory and learning. *J. Verbal Learning Verbal Behav.* 12, 543–550.
46. Larrabee, G.J., Trahan, D.E., and Levin, H.S. (2000). Normative data for a six-trial administration of the Verbal Selective Reminding Test. *Clin. Neuropsychol.* 14, 110–118.
47. Benedict, R.H. (1995). *The Brief Visuospatial Memory Test-Revised (BVRT-R): Manual*. Psychological Assessment Resources, Inc.: Lutz, FL.
48. Smith, A. (1982). *Symbol Digit Modalities Test (SDMT) Manual (Revised)*. Western Psychological Services: Los Angeles.
49. Delis, D.C., Kaplan, E., and Kramer, J.H. (2001). *Delis-Kaplan Executive Function System*. The Psychological Corporation: San Antonio, TX.
50. Stroop, J.R. (1935). Studies of interference in serial verbal reactions. *J. Exp. Psychol.* 18, 643–662.

51. Strong, C.A., Tiesma, D., and Donders, J. (2011). Criterion validity of the Delis-Kaplan Executive Function System (D-KEFS) fluency subtests after traumatic brain injury. *J. Int. Neuropsychol. Soc.* 17, 230–237.
52. Binder, L.M., and Rohling, M.L. (1996). Money matters: a meta-analytic review of the effects of financial incentives on recovery after closed-head injury. *Am. J. Psychiatry* 153, 7–10.
53. McCauley, S.R., Boake, C., Pedroza, C., Brown, S.A., Levin, H.S., Goodman, H.S., and Merritt, S.G. (2008). Correlates of persistent postconcussional disorder: DSM-IV criteria versus ICD-10. *J. Clin. Exp. Neuropsychol.* 30, 360–379.
54. Paniak, C., Reynolds, S., Toller-Lobe, G., Melnyk, A., Nagy, J., and Schmidt, D. (2002). A longitudinal study of the relationship between financial compensation and symptoms after treated mild traumatic brain injury. *J. Clin. Exp. Neuropsychol.* 24, 187–193.
55. Cato, M.A., Brewster, J., Ryan, T., and Giuliano, A.J. (2002). Coaching and the ability to simulate mild traumatic brain injury symptoms. *Clin. Neuropsychol.* 16, 524–535.
56. Miller, L. (2001). Not just malingering: syndrome diagnosis in traumatic brain injury litigation. *NeuroRehabilitation* 16, 109–122.
57. Larrabee, G.J. (1997). Neuropsychological outcome, post concussion symptoms, and forensic considerations in mild closed head trauma. *Semin. Clin. Neuropsychiatry* 2, 196–206.
58. Carroll, L.J., Cassidy, J.D., Peloso, P.M., Borg, J., von Holst, H., Holm, L., Paniak, C., and Pepin, M. (2004). Prognosis for mild traumatic brain injury: results of the WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury. *J. Rehabil. Med. Suppl* 43, 84–105.
59. Hou, R., Moss-Morris, R., Peveler, R., Mogg, K., Bradley, B.P., and Belli, A. (2012). When a minor head injury results in enduring symptoms: a prospective investigation of risk factors for post-concussional syndrome after mild traumatic brain injury. *J. Neurol. Neurosurg. Psychiatry* 83, 217–223.
60. McCrea, M., Guskiewicz, K.M., Marshall, S.W., Barr, W., Randolph, C., Cantu, R.C., Onate, J.A., Yang, J., and Kelly, J.P. (2003). Acute effects and recovery time following concussion in collegiate football players: the NCAA Concussion Study. *JAMA* 290, 2556–2563.
61. Peterson, C.L., Ferrara, M.S., Mrazik, M., Piland, S., and Elliott, R. (2003). Evaluation of neuropsychological domain scores and postural stability following cerebral concussion in sports. *Clin. J. Sport Med.* 13, 230–237.
62. Maddocks, D., and Saling, M. (1996). Neuropsychological deficits following concussion. *Brain Inj.* 10, 99–103.
63. Scheid, R., Walther, K., Guthke, T., Preul, C., and von Cramon, D.Y. (2006). Cognitive sequelae of diffuse axonal injury. *Arch. Neurol.* 63, 418–424.
64. Bazarian, J.J., Zhong, J., Blyth, B., Zhu, T., Kavcic, V., and Peterson, D. (2007). Diffusion tensor imaging detects clinically important axonal damage after mild traumatic brain injury: a pilot study. *J. Neurotrauma* 24, 1447–1459.
65. Messé, A., Caplain, S., Paradot, G., Garrigue, D., Mineo, J.F., Soto Ares, G., Ducreux, D., Vignaud, F., Rozec, G., Desal, H., Pelegrini-Issac, M., Montreuil, M., Benali, H., and Lehericy, S. (2011). Diffusion tensor imaging and white matter lesions at the subacute stage in mild traumatic brain injury with persistent neurobehavioral impairment. *Hum. Brain Mapp.* 32, 999–1011.
66. Messé, A., Caplain, S., Pelegrini-Issac, M., Blanco, S., Montreuil, M., Levy, R., Lehericy, S., and Benali, H. (2012). Structural integrity and postconcussion syndrome in mild traumatic brain injury patients. *Brain Imaging Behav.* 6, 283–292.

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