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Mild traumatic brain injuries with loss of consciousness are associated with increased inflammation and pain in military personnel

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ABSTRACT

Mild traumatic brain injuries (mTBI) are a pervasive concern for military personnel. Determining the impact of injury severity, including loss of consciousness (LOC) may provide important insights into the risk of psychological symptoms and inflammation commonly witnessed in military personnel and veterans following mTBI. US military personnel and veterans were categorized into three groups; TBI with LOC (n = 36), TBI without LOC (n = 25), Controls (n = 82). Participants reported their history of mTBI, psychological symptoms (post-traumatic stress disorder [PTSD] and depression), health-related quality of life (HRQOL), and underwent a blood draw. ANCOVA models which controlled for insomnia status and combat exposure indicated that both mTBI groups (with/without LOC) reported significantly greater depression and PTSD symptoms compared to controls; however, they did not differ from each other. The mTBI with LOC did report greater pain than both controls and mTBI without LOC. The TBI with LOC group also had significantly elevated IL-6 concentrations than both TBI without LOC and control groups. Within the mTBI groups, increased TNFα concentrations were associated with greater PTSD symptoms. These findings indicate that sustaining an mTBI, with or without LOC is detrimental for psychological wellbeing. However, LOC may be involved in perceptions of pain and concentrations of IL-6.

1. Introduction

Recent deployments have resulted in a substantial increase in military personnel sustaining traumatic brain injuries (TBIs). The majority of these TBIs are classified as mild (mTBI), which may or may not include a period of up to 30 min of loss of consciousness (LOC) (Terrio et al., 2009). Following an mTBI, full recovery is expected within days or weeks however, some individuals experience symptoms and deficits for months or even years following the injury. Developing a better understanding of which military personnel are at risk for poorer outcomes and recovery is essential. Identifying biomarkers that relate to this risk may provide greater insights for monitoring and intervention.

Traumatic brain injuries have been associated with a range of negative psycho-social and health outcomes including post-traumatic stress disorder (PTSD) (Combs et al., 2015), depression (Koponen et al., 2002), sleep disturbances (Mysliwiec et al., 2013), and post-concussive symptoms (Schneiderman et al., 2008). Experiencing such outcomes, has been shown to impede recovery, delay return to service, and has been associated with significant declines in overall quality of life (QOL) (Armed Forces Health Surveillance Center, 2010; Capaldi et al., 2011). As such there are significant health and fiscal benefits to understanding the factors associated with individual recovery following mTBI. In recent years, exploring if there are additive negative psychosocial or health effects due to the presence of a period of LOC with mTBI has gained attention. A recent study found a stepwise increases in having multiple negative health outcomes as TBI severity increased, especially for disability, poor life satisfaction, and memory impairment (Whiteneck et al., 2016). Compared to a group with no injury, the adjusted prevalence ratio for disability status was 1.80 for mTBI without LOC, and 2.29 for the mTBI with LOC group (Whiteneck et al., 2016). A study of military personnel with mTBI, reported that of those who experienced LOC, 43.9% met criteria for PTSD compared with 27.3% who reported only alterations in mental status (Hoge, 2008). Furthermore, LOC has been found to be an independent predictor of depression (Hoge, 2008). However, the role of LOC in symptom maintenance and severity remains unclear.

Acutely post-injury the body's immune response begins by

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producing pro-inflammatory (e.g. interleukin [IL]-6, and tumor necrosis factor-alpha [TNFα]) and anti-inflammatory (e.g., −10) cytokines (Hernandez-Ontiveros et al., 2013; McKee and Lukens, 2016). Initially this process is essential for recovery, however, this process can become dysregulated. Dysregulation is associated with poor recovery and even fatalities in patients following severe TBIs (Ferreira et al., 2014; Schneider Soares et al., 2012). To date, there are few studies which examined if this dysregulation occurs in mTBI and no study has explored if LOC impacts on cytokine expression. Findings from preclinical models have indicated that peripheral inflammation from mTBI is associated with behavioral deficits (Collins-Praino et al., 2018; Gao et al., 2017). One recent study from our lab showed IL-6 and TNF-α was higher in participants with mTBI compared to those without a history of TBI and these biomarkers were also significantly correlated with PTSD symptoms (Devoto et al., 2017). However, examining if the presence of LOC results in increased dysfunction is unexplored.

This study of active duty military personnel, aimed to examine if mTBI, with or without LOC, is associated with increased prevalence of PTSD, depression, and HRQOL symptoms, as well as altered cytokine levels, compared to personnel who did not sustain a TBI in recent combat. We hypothesized that military personnel who sustained a TBI with LOC would have more psychological symptoms (PTSD and depression), reductions in HRQOL and heightened inflammatory cytokines in comparison to TBI without LOC and controls (no history of TBI).

2. Methods

The Institutional Review Board #145947 at Madigan Army Medical Center in Tacoma, Washington approved this study. Written informed consent was provided by each participant prior to study participation.

2.1. Participants

Participants were 144 U.S active duty military personnel, from a larger military cohort referred for sleep difficulties to the Madigan Sleep Disorders Clinic. The methods have been detailed previously (Mysliwiec et al., 2013), however briefly, all participants underwent a sleep medicine evaluation and diagnostic polysomnogram. Inclusion for this study was that participants had returned from deployment within 18 months prior to study participation. Exclusion criteria included; 1) no ongoing treatment, or military administrative actions regarding drug or alcohol abuse, 2) current serious medical condition (i.e. autoimmune disorders, cancer, diabetes) or current unstable psychiatric condition (i.e. bipolar, schizophrenia), and 3) severe neurological disorder (i.e. stroke history, multiple sclerosis, seizure disorder). Participants provided demographic information including, their military status and also their combat experience using The Combat Experiences Scale (CES) (Vogt et al., 2008). The total score ranges from 0 to 15, with higher scores indicating more varied combat-related exposures on one or more occasions. Height and weight were also measured to provide a body mass index (BMI) score, as BMI has been shown to be associated with inflammation. Participants also self-reported their sleep difficulties. Sleep diagnoses were classified in accordance with the International Classification of Sleep Disorders, second edition (ICSD-2) (Thorpy, 2012). Participants were classified as having primary insomnia if they reported one or more sleep-related complaints including but not limited to difficulty initiating sleep, maintaining sleep, or sleep that is chronically nonrestorative, and with at least one of the associated symptoms of daytime impairment. Obstructive sleep apnea (OSA) was diagnosed if the participant's PSG demonstrated apneas or hypopneas with an apnea-hypoxia index (AHI) >5/h.

2.2. Measures

PTSD symptoms were assessed using the PTSD Checklist-Military (PCL-M) Version (Wilkins et al., 2011). The PCL-M has been shown to be a reliable and valid measure of PTSD severity (Wilkins et al., 2011). There are 17 questions with responses ranging from 1 "Not at all" to 5 "Extremely", with possible total scores ranging from 17 to 85. Higher scores are indicative of greater severity of PTSD.

Depression symptoms were assessed using The Quick Inventory of Depressive Symptomatology (QIDS), which is a reliable and valid tool for measuring major depressive disorder (Rush et al., 2003). The questionnaire consists of 16 questions and scores range from 0 to 27, with a higher score indicative of greater severity of depression symptoms.

HRQOL was assessed using the 36-Item Short Form Survey (SF-36) (Jenkinson et al., 1994). This 36-question measure consists of eight subscales: vitality, physical functioning, bodily pain, general health perception, physical role functioning, emotional role functioning, social role functioning, mental health. Higher scores, on each of the subscales, are indicative of better HRQOL.

2.3. Determining TBI with LOC groups

History of TBI and LOC were determined using the Warrior Administered Retrospective Casualty Assessment Tool (WARCAT), a self-report measure of deployment history and war-related injuries (Terrio et al., 2011). The WARCAT assesses war-related and post-deployment injuries by investigating the mechanisms of injury and evaluates immediate symptoms or loss of consciousness following the injury. Participants were classified as mTBI-positive (+) if during their most recent deployment they self-identified has having (1) sustained a blow to the head and/or head injury, and (2) reported any period of LOC and/or symptoms of concussion (i.e. "being dazed, confused, or seeing stars). Duration of LOC was self-reported on the WARCAT. The potential responses on the WARCAT for LOC duration is a) less than one minute, b) for 1–20 min or c) greater than 20 min. As LOC duration of less than 30 min is typically classified as mild according to the DOD (Terrio et al., 2009), any participant who endorsed "greater than 20 min" were removed from the analyses ($n = 1$). Controls were those participants who did not report a TBI during their most recent deployment and reported that they had "never" had a concussion or other head injury prior to this deployment. As such, participants were split into three groups in accordance with their TBI status and LOC duration; (1) *Controls;* no history of TBI or LOC ($n = 82$); (2) *TBI w/out LOC;* sustained a TBI at most recent deployment but no period of LOC ($n = 36$), (3) *TBI w LOC;* sustained a TBI at most recent deployment with a concurrent period of LOC of less than 20 min ($n = 25$).

2.4. Laboratory analysis

Non-fasting, blood plasma samples were drawn at Madigan Sleep Disorders Clinic and processed in accordance with standard procedures (Olivera et al., 2015). Aliquoted samples were stored at −80 °C. Samples were collected between 8:45 am and 3:50 pm ($M = 11$:36; SD = 1 h 56 mins). It is noted that time of sample collection and cytokine concentrations of TNFα, IL-6 and IL-10 were not significantly correlated ($p = 0.635$, 0.200, and 0.863 respectively). Cytokines were measured using the Simoa™ high definition-1 (HD-1) technology, an ultra-sensitive assay that can detect protein levels in peripheral blood. Cytokines were quantified using the Cytokine 3-Plex assay kit (Quanterix, Lexington, MA) for simultaneous measurement of TNFα, IL-6 and IL-10. The assays were run in duplicate and samples were blinded to experimenters. The lower limit of detection for TNFα, IL-6 and IL-10 was 0.126 pg/mL, 0.330 pg/mL and 0.034 pg/mL, respectively. The intra- and inter-assay coefficient of variation (CV) values were less than 10%.

Table 1
Demographics of the sample.

	Controls	TBI		F/χ^2	p
		w/out LOC	w LOC		
	$N = 82$	$N = 36$	$N = 25$		
Age (years); mean (SD)	32.7 (7.1)	33.1 (9.1)	33.0 (9.2)	0.05	0.953
Gender (Male); no. (%)	77 (94)	36 (100)	25 (100)	3.85	0.146
Race; no. (%)				8.19	0.770
White	49 (60)	25 (69)	16 (64)		
Black	12 (14)	3 (8)	1 (4)		
Asian	5 (6)	1 (3)	1 (4)		
Pacific Islander	5 (6)	1 (3)	2 (8)		
Native American	1 (1)	–	–		
Mixed Race	3 (4)	4 (11)	3 (12)		
Other/Unknown	7 (9)	2 (6)	2 (8)		
Marital Status; no. (%)				4.87	0.561
Single	11 (13)	4 (13)	2 (8)		
Married	60 (73)	26 (71)	16 (65)		
Separated	5 (6)	3 (8)	5 (19)		
Divorced	6 (8)	3 (8)	2 (8)		
BMI; mean (SD)	29.6 (4.3)	28.9			
(4.4)	30.2 (4.0)	0.75	0.474		
Service Branch; no. (%)				2.27	0.686
Army	77 (94)	33 (91)	25 (100)		
Air Force	4 (5)	2 (6)	–		
Navy	1 (1)	1 (3)	–		
Military Rank; no. (%)				0.76	0.944
NCO	40 (55)	16 (50)	14 (61)		
Officer	5 (6)	2 (6)	1 (4)		
Junior	28 (38)	14 (44)	8 (35)		
Combat Exposure; mean (SD)	5.6 (3.8)	7.9 (3.9)	9.4 (4.1)	11.02	< 0.001
Number of Deployments; median (IQR)	2.0 (1.0–3.0)	2.0 (1.0–3.0)	2.0 (1.0–2.5)	1.48	0.231
Number of prior concussions; median (IQR)	–	1 (0–2)	0 (0–3)	0.08	0.894
Time since last deployment (>6months); no., (%)	58 (71)	29 (81)	20 (80)	1.71	0.425
Insomnia (Yes); no. (%)	29 (36)	23 (66)	18 (72)	14.35	0.001
OSA (Yes); no. (%)	47 (65)	17 (52)	17 (68)	2.25	0.324

Note: SD – Standard deviation; no – number; BMI – Body Mass Index; OSA – Obstructive Sleep Apnea.

2.5. Statistical analysis

All statistical analyses were conducted using Statistical Package for the Social Sciences (SPSS software version 22.0; IBM SPSS Inc.). Analysis of variance (ANOVA) and Chi-squared analysis were used to identify group differences on the key demographic variables. Analysis of Covariance (ANCOVA) was also performed to identify group differences on the main outcome variables, controlling for significant group differences on insomnia prevalence and CES history. Post-hoc analyses were conducted applying a Bonferroni adjustment for multiple comparisons; all analyses had a significance level of $p < 0.05$. To determine if any of the cytokines were significantly associated with psychological symptom severity in participants with a history of TBI, Pearson's correlations were conducted.

3. Results

3.1. Sample characteristics

Demographic and military characteristics of the sample are provided in Table 1. The majority of the sample were white (63%) and male (97%). Participants in this study returned from deployment between 3- and 18-months prior to study participation. Across the groups there were no significant differences on the number of deployments, time since deployment, or military rank, however combat exposure did significantly differ. Post-hoc analysis indicated that both the TBI w LOC and TBI w/out LOC groups had significantly higher combat exposure scores than controls ($p < 0.001$ and $p = 0.008$, respectively), however they did not significantly differ from each other ($p = 0.489$). The groups did not significantly differ for presence of OSA ($p = 0.324$), however they did significantly differ on prevalence of insomnia ($\chi^2 = 14.35, p = 0.001$). In accordance with z-proportional differences, the control group had significantly lower prevalence of insomnia compared to the two mTBI groups, however, the mTBI groups did not significantly differ.

3.2. Group analysis of psychological outcomes and QOL

Table 2 illustrates group differences on PTSD and depression. The overall ANCOVA models were significant for PTSD and depression symptoms ($p < 0.001$ and $p < 0.001$, respectively). PTSD symptoms significantly differed across the groups, even after controlling for CES and insomnia status ($p < 0.001$). The control group had significantly lower reported PTSD symptoms than both TBI groups. TBI w LOC and TBI w/out LOC did not significantly differ. This pattern of responses across the groups was similar for depression symptoms ($p = 0.001$). Within the PTSD model, both insomnia status and CES were significant predictors of PTSD symptom severity ($p = 0.005$, and $p = 0.003$, respectively). Within the depression model, only insomnia status was a significant predictor ($p = 0.001$).

ANCOVA analysis indicated that there were significant group differences for all eight sub-scales of HRQOL. As seen in Table 3, in all analyses, the control group reported significantly higher HRQOL than both TBI groups, even after controlling for CES and insomnia status.

Table 2
Group differences on PTSD and depression.

	PTSD			Depression		
	F	p	η_p^2	F	p	η_p^2
Insomnia	8.14	0.005	0.057	12.13	0.001	0.083
CES	9.25	0.003	0.065	2.31	0.131	0.017
TBI Group	12.87	<0.001	0.161	7.19	0.001	0.097

Note: η_p^2; partial eta squared.

Table 3
Group differences for eight SF-36 subgroups.

	Emotional Wellbeing			Energy/Fatigue			General Health Perception			Pain		
	F	*p*	η_p^2	*F*	*p*	η_p^2	*F*	*p*	η_p^2	*F*	*p*	η_p^2
Insomnia	11.42	0.001	0.080	7.74	0.006	0.055	7.74	0.006	0.055	5.53	0.020	0.040
CES	1.16	0.284	0.009	0.21	0.652	0.002	0.85	0.359	0.006	1.35	0.247	0.010
TBI Group	4.90	0.009	0.069	7.78	0.001	0.105	7.29	0.001	0.100	6.12	0.003	0.084

	Physical Function			Personal/Emotional Problems			Physical Health Problems			Social Functioning		
	F	*P*	η_p^2	*F*	*P*	η_p^2	*F*	*p*	η_p^2	*F*	*p*	η_p^2
Insomnia	3.68	0.057	0.027	8.71	0.004	0.066	5.74	0.018	0.042	9.00	0.003	0.064
CES	0.11	0.740	0.001	1.66	1.99	0.012	1.25	0.265	0.009	4.71	0.032	0.034
TBI Group	3.92	0.022	0.056	4.66	0.011	0.066	8.49	< 0.001	0.114	8.66	< 0.001	0.116

Note: η_p^2; partial eta squared.

There were no significant differences between the TBI w LOC and TBI w/out LOC for symptom severity on the SF-36, except for the subscale of pain. Self-reported pain was significantly greater in the TBI w LOC group compared to both the TBI w/out LOC ($p = 0.024$) and controls ($p = 0.002$). Pain severity did not differ between TBI w/out LOC and controls ($p = 1.00$). Finally, the difference between TBI w LOC and TBI w/out LOC on physical functioning was trending towards significance ($p = 0.062$). Across each of these ANCOVA models, CES was a significant predictor of social functioning only. In contrast, insomnia status was significantly associated with worse SF-36 scores on all subscales, except physical functioning ($p = 0.057$).

3.3. Group analysis of biomarkers of inflammation

ANCOVA models were used to examine if there were differences across the groups on IL-6, −10, and TNFα, controlling for insomnia status and CES. For IL-6, the model was significant ($F_{(4126)} = 7.67$, $p < 0.001$), even after controlling for CES and insomnia status. Post-hoc analyses indicated that IL-6 was elevated in the TBI w LOC group compared to both the TBI w/out LOC and control groups ($p < 0.001$ for both comparisons). IL-6 concentrations did not differ between the TBI w/out LOC and control groups ($p = 1.00$). Insomnia status was a significant predictor of IL-6 concentrations in this model ($F_{(1126)} = 4.17$, $p = 0.043$), however, CES was not significant ($p = 0.326$). Presence of insomnia was associated with an 0.37 pg/ml increase in IL-6 concentrations compared to no insomnia. The ANCOVA models for both IL-10 and TNF-α did not reach statistical significance ($F_{(4128)} = 1.46$, $p = 0.219$, $F_{(4127)} = 1.28$, $p = 0.281$, respectively).

As the mTBI groups reported significantly greater symptom severity, regardless of LOC, we wanted to determine if there were any correlation between IL-6, −10 and TNFα and symptom severity in participants with a history of mTBI ($n = 54$). The mTBI groups did not significantly differ in insomnia status or CES, therefore, these variables were not controlled for in this analysis. Increased concentrations of TNFα were associated with greater PTSD symptom severity ($r = 0.36$, $p = 0.005$). There were no other associations found between the cytokines and the psychological and HRQOL outcomes.

4. Discussion

Here, we report that mTBIs with an associated period of LOC (< 20mins), are associated with elevations in IL-6 concentrations and pain symptom reporting, over and above that of TBIs without LOC and controls. However, contrary to our predictions, sustaining any form of mTBI (with or without LOC) was associated with greater PTSD and depression symptoms, as well as declines in all eight domains of HRQOL compared to controls. These findings provide insights into the psychological and inflammatory consequences of TBIs that are related to health morbidity and mortality. Furthermore, these finding suggests that, in military personnel, inflammation may be exacerbated by LOC rather than the TBI itself which may provide insights into the role of LOC in inflammation.

This paper supports previous research that link TBIs to higher rates of depression and PTSD (Vasterling et al., 2017b). Previous research found that "being knocked out" was linked to greater risk of PTSD in military personnel (Vasterling et al., 2017a), in this study, participants who had sustained a TBI with LOC did not have greater PTSD and depression symptoms. However, sustaining a TBI both with and without LOC were associated with significantly greater PTSD and depression symptoms in comparison to controls with no history of TBI. One factor that was observed to be affected by LOC was pain severity. Participants who sustained an mTBI with LOC had the highest reported pain (indicated by lowest score on the SF-36), which was significantly greater than both the mTBI without LOC and control groups. Furthermore, there was no difference between the mTBI without LOC and control group, indicating that LOC has an effect on exacerbating pain symptoms, even after controlling for insomnia status and CES. This difference may be due to the severity of injury, which is consistent with other studies which report a positive association between pain and TBI severity (Hoge et al., 2008; Kay et al., 1971). In a survey of 2525 military personnel, participants who sustained LOC (< 30 mins) reported significantly more bodily pain than those who had sustained other non-TBI related injuries (Hoge et al., 2008). However, whether bodily pain, results from the increased injury severity, the violent trauma in which the TBI may have occurred, and/or due to underlying pathophysiology remains to be determined (Kirshblum et al., 2011; Nampiaparampil, 2008).

Our finding of elevated IL-6 concentrations in TBI with LOC supports previous research which showed that IL-6 is implicated in recovery from TBIs. All participants in this study had sustained a TBI within their last deployment, and for the majority (~80%) had returned from deployment greater than 6 months prior to testing. Thus, this finding may suggest that having a TBI with LOC is associated with immune dysregulation which has consequences overtime. Chronic inflammation, including elevated inflammatory cytokines have been linked to cell death, microglial activation, axonal and astroglial dysfunction, and increased permeability of the blood-brain-barrier (Brown and Vilalta, 2015; Kim et al., 2015). IL-6 elevations have also been linked to increased health risks such as obesity, cardiovascular disease (Yudkin et al., 2000), and mortality (Harris et al., 1999; Stensballe et al., 2009). Furthermore, IL-6 concentrations have been linked to psychological and behavioral symptoms including, PTSD and depression (Devoto et al., 2017; Licastro et al., 2016). A recent study of active duty military and veterans who had sustained a mTBI, found that PTSD was associated increased IL-6 concentrations (Devoto et al., 2017). Taken together, this research indicates that IL-6, may be an important indicator of dysregulation and may be particularly important to monitor following TBIs with LOC. Examining the longitudinal effects of these heightened patterns following mTBI with LOC is needed.

We also report that higher TNFα is associated with increased PTSD symptomology for participants with a history of TBI. This supports prior research, including a recent review which indicated that plasma/serum levels of TNFα were consistently elevated in participants with PTSD compared to healthy controls (Hussein et al., 2017). TNFα plays a key role in immune-regulation, it has been associated with stress and several psychiatric disorders, including, depression and Alzheimer's disease (Himmerich et al., 2015, 2016; Schmidt et al., 2014). As such, it has been suggested that TNFα may be a biomarker of PTSD and psychopathology more generally. In accordance with the findings of this study, TNFα may be a marker of PTSD symptomology in those who have sustained an mTBI. However, additional work to elucidate the direction of association and role of cytokines such as TNFα in PTSD, is needed. Pre- and post-deployment measures may provide significant insights as to the role of injury and everyday stressors experienced as part of military life (e.g. poor sleep and shift work conditions) which may affect the trajectory of both PTSD symptoms and cytokines.

Sleep disturbances are highly prevalent following TBI, with approximately 50% of all individuals suffering from clinically significant sleep disturbances following their injury (Mathias and Alvaro, 2012). Disrupted sleep is associated with a wide range of health, social and economic costs that may prolong TBI recovery and reduce quality of life (Hossain and Shapiro, 2002). The results of this study indicated that insomnia status was significantly associated with greater PTSD and depression symptoms, declines in all but one of the HRQOL subscales (physical functioning; $p = 0.057$), and was associated with increased IL-6 concentrations. This supports an abundance of research which indicates poor sleep leads to worse psycho-social and health outcomes. This is particularly pertinent in military personnel who are already at high risk of sleep disorders such as insomnia (Mysliwiec et al., 2013). Indeed, a recent study found that veterans with TBI and PTSD reported more severe insomnia status and worse quality of life due to poor sleep (Balba et al., 2018). Although we are unable to determine if insomnia preceded the TBI and/or symptoms our findings indicate that it is vital to consider sleep when examining TBI outcomes.

This study was limited by the reliance on self-reported assessment to determine mTBI and symptoms. Further this study includes a relatively small, cross-sectional sample who were seeking treatment at a sleep clinic. Whilst sleep problems are prevalent in the wider military context (Mysliwiec et al., 2013), further research is needed to ensure that the findings of this study can be generalized more widely to both military and civilian populations. Thus, additional longitudinal research is needed to elucidate the role of LOC on symptom perturbation, maintenance, and cytokine regulation. Furthermore, imaging such as CT and/or MRI would be beneficial to identify if the outcomes observed in this study are a result of severity of injury. The results of this study highlight, that mTBI with LOC may complicate recovery through exacerbating pain symptoms and affecting the regulation of IL-6. Further, we have supported a wealth of studies which show that TBI, regardless of LOC duration, affects psychological outcomes. To improve outcomes, management, and treatment of mTBI in the military and veteran population, longitudinal research that accounts for both mTBI with and without LOC is vital.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2019.07.001.

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