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A case–control study examining whether neurological deficits and PTSD in combat veterans are related to episodes of mild TBI

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ABSTRACT

Background: Mild traumatic brain injury (mTBI) is a common injury among military personnel serving in Iraq or Afghanistan. The impact of repeated episodes of combat mTBI is unknown.

Objective: To evaluate relationships among mTBI, post-traumatic stress disorder (PTSD) and neurological deficits (NDs) in US veterans who served in Iraq or Afghanistan.

Methods: This was a case–control study. From 2091 veterans screened for traumatic brain injury, the authors studied 126 who sustained mTBI with one or more episodes of loss of consciousness (LOC) in combat. Comparison groups: 21 combat veterans who had definite or possible episodes of mTBI without LOC and 21 veterans who sustained mTBI with LOC as civilians.

Results: Among combat veterans with mTBI, 52% had NDs, 66% had PTSD and 50% had PTSD and an ND. Impaired olfaction was the most common ND, found in 65 veterans. The prevalence of an ND or PTSD correlated with the number of mTBI exposures with LOC. The prevalence of an ND or PTSD was >90% for more than five episodes of LOC. Severity of PTSD and impairment of olfaction increased with number of LOC episodes. The prevalence of an ND for the 34 combat veterans with one episode of LOC (4/34=11.8%) was similar to that of the 21 veterans of similar age and educational background who sustained civilian mTBI with one episode of LOC (2/21=9.5%, p-NS).

Conclusions: Impaired olfaction was the most frequently recognised ND. Repeated episodes of combat mTBI were associated with increased likelihood of PTSD and an ND. Combat setting may not increase the likelihood of an ND. Two possible connections between mTBI and PTSD are (1) that circumstances leading to combat mTBI likely involve severe psychological trauma and (2) that altered cerebral functioning following mTBI may increase the likelihood that a traumatic event results in PTSD.

ARTICLE SUMMARY

Article focus

- Case–control study of mTBI associated with LOC among US veterans who were deployed to Iraq or Afghanistan during Operations Iraqi Freedom and Enduring Freedom.
- Three study groups: (1) 126 veterans who had mTBI with LOC, (2) 21 OIF/OEF veterans who did not suffer mTBI with LOC and (3) 21 veterans who sustained mTBI with LOC in a civilian setting.
- Evaluated NDs including a quantitative test of olfaction, PTSD with severity assessed using the PCL-M instrument and a cognitive function using the Montreal Cognitive Assessment Test.

Key messages

- Olfaction was a sensitive test for neurological injury associated with mTBI with LOC.
- More episodes of mTBI with LOC were associated with higher prevalence rates of NDs or of PTSD.
- The severity of PTSD and extent of olfactory impairment increased with the number of episodes of LOC; cognitive function performance was inversely related to the number of episodes of LOC.

Strengths and limitations of this study

- Case–control study of US combat veterans with mTBI who were assessed for NDs, PTSD and cognitive function.
- Subjects and comparison groups had detailed assessments for NDs, and combat veterans were also assessed for PTSD.
- The findings should be relevant to other groups of military personnel with combat mTBI.
- The neurological examination was not blinded.
- The selection of veterans in this study may be biased because veterans who do not have health issues may not seek care from the Department of Veterans Affairs.
- The comparison groups were small.
- The findings in veterans with mTBI with LOC may not apply to people with mTBI without LOC.

INTRODUCTION

Traumatic brain injury (TBI) is a major worldwide cause of death and disability. The worldwide incidence is about 10 million cases per year.[1] This is likely an underestimate of the true incidence because cases of mild traumatic brain injury (mTBI) are often unreported. In the USA, TBI is the most common neurological diagnosis leading to treatment in emergency/urgent care facilities with about 1 million cases of TBI yearly and 50 000 deaths per year.[2] Most studies of TBI focus on moderate to severe TBI, and there are relatively few studies of TBI incurred in military combat. mTBI, or concussion, is a common military injury among NATO troops serving in Iraq and Afghanistan (OIF/OEF).[3] When US Army troops were evaluated after a deployment to Iraq, between 15% and 20% reported at least one episode of TBI, predominantly mTBI.[4–6] In a study of US National Guard soldiers who were deployed to Iraq, when queried 1 month before the end of a deployment, 9.2% of soldiers reported an mTBI during the deployment and 22.0% reported an mTBI during the deployment when queried 1 year later.[7] The cause for the delay in self-recognition of mTBI is uncertain. Several factors may increase reporting of mTBI after deployment. 'Over time, retrospective recall of combat events and history of concussion/mTBI may be influenced by current symptoms of distress, attributions about current psychosocial difficulties and secondary gain.'[7] Alternatively, mTBI may be under-reported during a deployment. 'While in theater, soldiers may minimize reports of concussion/mTBI history to remain with their units, live up to perceived expectations of superiors and peers, and ensure health concerns do not delay return home during demobilization.'[7]

Combat produces psychologically traumatic events; hence, stress reactions including post-traumatic stress disorder (PTSD) frequently accompany mTBI.[4 8] The presence of some post-concussion symptoms such as impaired memory appears to correlate more strongly with the presence of PTSD rather than with mTBI.[4 7] However, post-traumatic headaches seem to be more strongly associated with mTBI.[4] The prevalence of neurological deficits (NDs) associated with combat mTBI and the relationships among ND, PTSD and number of episodes of mTBI are unknown.

In this case-controlled observational study, we screened 2091 OIF/OEF veterans and identified 126 veterans who had one or more episode of combat mTBI associated with loss of consciousness (LOC). The research questions we examined were (1) what are the most frequently recognised NDs that can be identified during an examination performed in a clinic setting? (2) Do associations exist between the episodes of TBI and NDs or PTSD? We evaluated veterans for NDs and PTSD and correlated outcomes with LOC episodes. We had two comparison groups. To evaluate whether episodes of mTBI with LOC differed from mTBI without LOC, we compared the findings in combat veterans who experienced mTBI episodes with LOC to combat veterans who did not have any LOC episodes. To consider if a combat setting influenced the likelihood of a veteran having residual NDs, we compared the findings in combat veterans who experienced mTBI episodes with LOC to veterans who suffered mTBI with LOC as civilians. The veterans in the comparison groups had the same testing as the veterans who had combat mTBI with LOC, which led to the smaller sizes of the comparison groups relative to the study group.

MATERIAL AND METHODS

This was a case-controlled observational study of a cohort of OIF/OEF veterans with mTBI that began as a Neurology Service Quality Assurance Monitor of the evaluation of OIF/OEF veterans with mTBI. We collected information from the veterans in an unblinded, but uniform and prospective, manner. Veterans did not sign consent forms. Data were collected at the Louis Stokes Department of Veterans Affairs Medical Center in Cleveland (CVAMC), which is a regional Polytrauma Center that addresses the needs of OIF/OEF veterans for most of the State of Ohio. The CVAMC Institutional Review Board reviewed the data in this report, approved waiver of HIPAA authorisation, granted a waiver of informed consent and approved submission of the data in this manuscript for publication.

There were three study groups: (1) 126 OIF/OEF veterans with one or more episode of LOC due to combat mTBI, (2) 21 OIF/OEF veterans who had no episodes of LOC and (3) 21 veterans who sustained an episode of mTBI with LOC as civilians.

mTBI criteria

mTBI criteria was an episode of TBI with LOC <30 min, duration of any alteration in consciousness (AOC) following the TBI was <24 h and post-traumatic amnesia (PTA) was <24 h.[9] We focused on veterans who had LOC because TBI depended upon historical recall. In a combat setting, it can be difficult to distinguish AOC from conflict-induced changes in arousal or emotion.

We defined combat mTBI as occurring (1) during engagement with enemy or (2) associated with an explosion from an enemy device such as mortar/artillery shell, rocket-propelled grenade, improvised explosive device or bomb. Non-combat TBI occurred during a deployment without enemy engagement or an explosion.

Subject selection—OIF/OEF veterans

The OIF/OEF veterans were individuals who sought care from the Veterans Health Administration of the United States (VHA) often for issues not related to TBI such as treatment of musculoskeletal pain or choosing VHA to be their personal health resource. In addition, many individuals had mental health issues such as depression and PTSD. OIF/OEF veterans were screened for TBI using a three-level sequential process. The first screening

step was a four question screening tool that was administered to all OIF/OEF veterans treated by VHA.[10] For those who confirm OEF or OIF deployment and do not have a prior diagnosis of TBI, the instrument proceeds using four sequential question sets. The initial screen is negative if a person responds negatively to any question set. If the veteran affirms one or more possible answer in each section, the screen is positive. The four sections are (1) events that could heighten the risk of TBI such as explosion exposure; (2) immediate symptoms following the event including LOC, AOC or PTA; (3) new or worsening symptoms following the event and (4) current symptoms that are consistent with TBI. The natural history of mTBI is that most individuals with civilian mTBI not associated with an explosion have resolution of symptoms within 6 months.[11] The recovery pattern of combat mTBI associated with an explosion is that a greater fraction of individuals can have persisting post-concussion symptoms following mTBI; however, these individuals also have PTSD that is likely contributing to the persistence of symptoms.[12] The symptoms in the screen included alterations in cognition, behaviour, motor or sensory function, balance or coordination and the presence of pain including headache. During a 24-month period between 2006 and 2008, 2091 OIF/OEF veterans were screened with the four question TBI screening tool[10] and 385 screened positive (18.4%). The veterans who were screened were veterans who sought healthcare with VHA. Figure 1 is a flow chart indicating the steps in identification of study subjects. We have a breakdown of the reasons that veterans screened negative during a 6-month interval within the entire 24-month window that we considered. During that 6-month period, 2% of veterans who screened negative indicated no exposure to an event associated with TBI (first screen section), 29% indicated that they did not have symptoms following exposure to an event that could produce TBI (second screen section), 31% indicated that they did not develop new symptoms following a TBI (third screen section) and 38% indicated that they had symptoms following TBI but that they did not currently have symptoms associated with TBI (fourth screen section). Veterans identified on the first screen were encouraged to undergo a second-level evaluation including an interview and physical examination; 350 had second-level screening (90.9%). The second-level screening was consistent with TBI in 210 (60%) and 178 agreed to additional assessment (84.8%). Among the 178 veterans, 65 were initially interviewed by a nurse practitioner (TP), trained in TBI assessment, to determine if they had sustained an episode of TBI; she found that 42 (64.6%) had histories of mTBI with LOC. The first author (RLR) performed a detailed assessment of the 113/178 veterans identified on the second-level screen and not evaluated by the nurse practitioner plus the 42 identified by the nurse practitioner, 155 veterans in total. This assessment typically took 2.5 h. It consisted of an interview, a structured neurological examination and a cognitive assessment test (described below). Veterans were asked, using open-ended questions, to describe what happened when they may have had TBI. Periods when the veteran was dazed or confused were considered as possible episodes of AOC. Periods when veterans could not remember what happened or had gaps in their memories for events before or after episodes of head trauma were considered to be PTA episodes. For each episode, LOC referred to a period when someone at the trauma scene observed the veteran to be unresponsive or the veteran did not move when prompted or nudged. If there were no observers, veterans could indicate an episode of LOC by stating that they clearly aroused or 'woke-up' following head trauma.

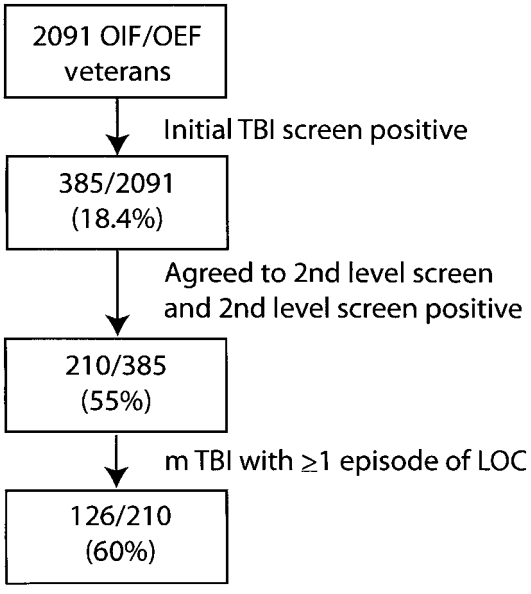

Figure 1 Flow chart of the selection of veterans with episodes of mild traumatic brain injury (mTBI) associated with loss of consciousness (LOC).

The 155 veterans evaluated by RLR were divided into two groups. One group contained 126 veterans who had one or more episode of combat mTBI with LOC. The second group contained 21 combat veterans who did not sustain LOC: 11 veterans with mTBI in a combat setting, five veterans who had mTBI in a non-combat setting and five veterans who did not have a definite episode of TBI. In the last su-group of five veterans, each veteran had at least one episode of exposure to an explosion that was associated with a behavioural change that RLR interpreted as possible but not definite episodes of AOC. The episodes in these five veterans may have been changes in arousal or emotion associated with combat rather than episodes of AOC. Thus, in this group of 21 veterans, 16 had episodes of mTBI associated with AOC and five had episodes that may have been mTBI. In comparisons, we considered both the group of 16 veterans who had definite episodes of mTBI without LOC and the larger

group of 21 veterans that included the five veterans who probably had mTBI without LOC. We excluded eight veterans who had moderate or penetrating TBI. The size of the comparison group of combat veterans with mTBI without LOC reflects the small fraction of veterans who did not have LOC among the 155 veterans examined by RLR. The 155 veterans examined by RLR had undergone two prior screening evaluations that indicated the veterans had mTBI with persisting residual symptoms such as headache. Seventy-nine/126 veterans (62.7%) who had combat mTBI with LOC and 12/21 (57.1%) who did not have LOC were National Guard or Reservists.

Veterans with civilian mTBI

We evaluated 36 veterans for TBI with LOC in a civilian environment. These veterans did not report prior episodes of TBI, including during military service. They were evaluated within 3 months of the mTBI. Thus, each veteran in this group experienced the first episode of mTBI as a civilian. We excluded 12 veterans because they did not have TBI—six, had moderate TBI—three, or because they were more than 65 years old—three. The age exclusion was because we did not expect to have combat veterans >65 years old. Etiologies of mTBI were motor vehicle accident (MVA)—eight, work-related TBI—seven (five falls), sporting—three, non-work fall—two, and assault—one.

Neurological examination

Neurological examination was previously described and included 50 scored elements (online appendix 1).[13] This examination included a screening test of cognitive function; cranial nerve testing; motor function testing, including assessment of tone, muscle bulk, strength and symmetry of movements; sensory function including sensation in the extremities and face and extinction of sensation with simultaneous stimulations; extremity coordination and precision of movement; stability of standing and gait. We included a 12-item quantitative olfactory test (Brief Smell Identification Test; Sensonics, Haddon Heights, New Jersey, USA, http://www.sensonics.com).[14] Each scent was evoked in a standardised manner, and the veteran identified the scent from a list of possibilities. The olfactory test had age-adjusted normal values.[15] Normal olfaction were scores ≥7/12 for <55 years old and ≥5/12 for ≥55 years old. We elicited no histories of impaired olfaction before OIF/OEF deployments. We chose the Montreal Cognitive Assessment (MOCA) Test to measure cognitive function because it is widely used within the Veterans Health Administration, it does not have a licensing fee and it has been used for repeated measures.[16] Performance on the MOCA is influenced by age and other demographic factors.[17] The median ages of the subjects in the three study groups indicate that the expected normal range of scores would be 26–30.[17] RLR administered the MOCA after obtaining the TBI history.

Every combat veteran was assessed for PTSD

Every combat veteran was assessed for PTSD using the Primary Care PTSD Screen (PC-PTSD).[18] The initial screen had four questions about PTSD symptoms. If a veteran acknowledged any three items, the screen was considered positive. Veterans who screened positive were assessed using a 17-item National Center for PTSD checklist for symptoms of military PTSD (PCL-M),[19] and the veterans were referred for further evaluation by a mental health professional qualified to diagnose PTSD. The mental health professional would often employ other PTSD evaluation instruments including the Mississippi Scale for Combat Related Posttraumatic Stress Disorder.[20] Each veteran had an interview to assess for the presence and severity of PTSD. Mental health professionals chose an interview instrument based upon their familiarity with the instrument and suitability to assessment of PTSD associated with military service. The most common interview instrument used was the Clinician Administered PTSD Scale.[21] Mental health professionals initiated treatment plans based upon assessment of the strengths of each veteran and the likeliness that a veteran would benefit from different treatment options.[22]

PTSD diagnosis satisfied the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, criteria of at least one intrusion item (eg, PCL-M questions 1–5), three avoidance (eg, PCL-M questions 6–12) and two hyper-arousal symptoms (eg, PCL-M questions 13–17).[19] Symptoms rated as 'moderately severe' or greater (responses three through five) were counted as present. In addition, the individual had to have substantial distress indicated by a PCL-M score of >50.[19]

Statistical methods

Independent variables were (1) mTBI episodes with LOC, (2) smoking history and (3) OIF/OEF deployment duration. Dependent variables were (1) NDs, (2) olfactory score, (3) presence of PTSD, (4) PCL-M score and (5) MOCA score. The primary outcome measures were two categorical variables: the presence of NDs and presence of PTSD. The secondary outcome measures were olfaction scores, PCL-M scores and MOCA scores. We studied the relationship between the prevalence of ND/PTSD and the number of LOC episodes. We also studied the relationship between the number of LOC episodes and MOCA scores, PCL-M scores or olfactory test results.

We compared the MOCA scores using the two-sided t test and olfaction scores using both the two-sided t test and the nonparametric Wilcoxon rank-sum test.[23] Outcome frequencies were analysed by Pearson's χ^2 test procedure or Fisher's exact test. In table 2, we evaluated the correlations between episodes of LOC and the presence of an ND or PTSD using generalised Spearman's rank correlation coefficients.[24] The correlations of MOCA, PCL-M and olfactory test scores and the numbers of episodes of LOC were evaluated using

Table 1 Frequencies of abnormalities on neurological testing, PTSD and MOCA scores for combat veterans with combat mTBI, combat veterans who did not have LOC and veterans who sustained mTBI in a civilian setting

Patient group	Deficit on neurological examination	Deficits on neurological examination other than olfaction	PTSD	MOCA scores
Combat veterans with mTBI (n=126)	65 (52%)	29 (23%)	83 (66%)	25.1±0.18
Combat veterans without LOC (n=21)*	0 (0%), p<0.001	0 (0%), p<0.001	2 (9.5%), p<0.001	28.8±0.29, p<0.001
Combat veterans with definite mTBI without LOC (n=16)*	0 (0%), p<0.001	0 (0%), p<0.001	1 (6.25%), p<0.001	28.9±0.32, p<0.001
Veterans with civilian mTBI (n=21)	2 (9.5%), p<0.001	1 (4.8%), p<0.001	1 (4.8%), p<0.001	28.4±0.23, p<0.001

Probabilities are for comparisons to combat veterans who sustained mTBI with LOC in combat.
*Sixteen had definite mTBI without LOC and five had probable mTBI without LOC.
LOC, loss of consciousness; MOCA, Montreal Cognitive Assessment; mTBI, mild traumatic brain injury; PTSD, post-traumatic stress disorder.

Kendall's rank correlation analysis.[23] Correlations of MOCA scores with PCL-M and olfaction scores were obtained using both Kendall's rank correlation analysis and Pearson's product–moment correlation coefficient.[23] The Bonferroni method was used to correct for multiple comparisons.[25] The Bonferroni p value ($p_{Bonferroni}$) adjusts the raw p value (p_{raw}) for the number of times that a hypothesis is tested (number of comparisons = m), $p_{Bonferroni} = m \cdot p_{raw}$. If the adjusted p value exceeds 1, it is set to 1. The Bonferroni test is conservative but always controls the familywise error rate. The probability values shown in tables 1 and 2 were corrected using the Bonferroni method. Values are presented as means ± SE of the mean.

RESULTS

The veteran groups had similar demographic features. The mean ages were combat veterans with LOC (n=126)—29.2±2.6 years (range 20–62 years), combat veterans without LOC (n=21)—30.0±1.6 years (range 21–48 years), and veterans with civilian mTBI (n=21)—35.1±2.2 years (range 21–53 years). The combat veterans older than 40 years were National Guard or Reservists. The percentages of women/high school graduates/college graduates were combat veterans with LOC—7.9/100/8.7, combat veterans without LOC—9.5/100/5, and veterans with civilian mTBI—9.5/100/9.5. The two groups of combat veterans had similar mean numbers of deployments/total deployment lengths: combat veterans with LOC—1.43±0.06 deployments (range 1–4 deployments)/81.4±3.2 weeks (range 40–208 weeks), and combat veterans without LOC—1.76±0.25 deployments (range 1–4 deployments)/90.8±12.0 weeks (range 40–208 weeks).

Veterans with combat-acquired mTBI with LOC had low MOCA scores and high frequencies of an ND and the presence of PTSD (table 1). ND were reduced olfaction—65, impaired balance—14, abnormal eye movements—13, motor asymmetry—two, and sensory change—two. Twenty-nine veterans had more than one ND. Among the 65 veterans with NDs, 36 (55%) had

Table 2 Correlations between the number of episodes of LOC and the presence of PTSD, presence of an ND, MOCA scores, PCL-M scores or olfactory test results for combat veterans

Correlation of episodes of mTBI with outcomes and correlation of PCL-M and olfaction tests scores with MOCA scores	mTBI associated with combat	
	Correlation coefficient	p Value
LOC vs ND (including olfaction)	0.314	<0.01
LOC vs ND (excluding olfaction)	0.254	<0.01
LOC vs PTSD	0.405	<0.01
LOC vs MOCA score	−0.226	<0.01
LOC vs PCL-M score	0.577	<0.01
LOC vs olfaction score	−0.665	<0.01
MOCA score vs PCL-M score	−0.620 (−0.765)	<0.001 for both
MOCA score vs olfaction score	0.00497 (0.0926)	NS for both
PCL-M vs olfaction	−0.194	NS

Kendall's rank correlation analysis coefficients are shown in the table with Pearson's product–moment correlation coefficients shown in parentheses.
LOC, loss of consciousness; MOCA, Montreal Cognitive Assessment; mTBI, mild traumatic brain injury; ND, neurological deficit; PTSD, post-traumatic stress disorder.

only impaired olfaction. Impaired balance was detected using the Romberg test.[26] The most frequently recognised abnormal eye movement was saccadic dysmetria (12 individuals), with one individual having asymmetric horizontal saccade velocity.[27] Motor asymmetry was detected with arm-rolling and upper extremity drift that were both present in two subjects.[28] The two veterans with sensory changes had extinction on simultaneous stimulation.

Half of the 126 veterans with combat mTBI had PTSD and an ND, 21 (17%) had PTSD without an ND, five (4%) had an ND without PTSD and 37 (29%) did not have PTSD or an ND. Among the 63 veterans with PTSD and an ND, mean MOCA scores were 24.0±0.26 and they were deployed 41.3±2.03 weeks, whereas veterans who did not have PTSD or an ND had higher MOCA scores (26.5±0.23, p<0.001) but similar durations of deployment, 38.8±3.09 weeks.

In contrast, 21 combat veterans who did not have LOC episodes had no NDs, a lower frequency of PTSD and higher MOCA scores (table 1). Their olfaction scores were higher than the 61 veterans who sustained mTBI with LOC without an ND, 11.1±0.17 vs 10.6±0.34 (p<0.01). The comparison group of 16 veterans who had definite episodes of mTBI without LOC also had a lower frequency of PTSD and higher MOCA scores (table 1). The olfaction scores of the group of 16 veterans were also higher than the scores of the veterans who had mTBI with LOC without an ND, 11.25±0.11 (p<0.01).

Because the most frequent ND was impaired olfaction, we considered other causes of olfactory impairment: smoking,[29] upper respiratory infection[30] and nasal sinus disease.[30] Smoking frequencies among combat veterans with or without NDs were similar (38.4% vs 39.34%, p-NS). Four veterans had upper respiratory congestion at the time of olfactory testing (1) or within the prior month (3). When retested 6–8 weeks later, the olfactory score for three veterans did not change. The score of the veteran with a symptomatic upper respiratory infection when initially tested improved to normal. The normal score was used for analysis. The frequencies of histories of nasal sinus disease were similar for veterans who had impaired olfaction (7.7%) versus those with normal olfaction scores (8.2%). Head imaging studies were not routinely done; however, 34 veterans with an ND (52.3%) and 31 veterans without an ND (50.8%) had an MRI or CT scan that visualised the sinuses. Four imaging studies for veterans with an ND (12%) and four for veterans without an ND (13%) revealed unilateral sinus disease. No individual had bilateral sinus findings.

Veterans with combat mTBI experienced 380 episodes of LOC, mean of 3.02±0.20 episodes of LOC per veteran (range of 1–8 episodes of LOC for a veteran, online appendix 2 shows the numbers of veterans with specific numbers of episodes of LOC). Most episodes of LOC were associated with an explosion. Explosions occurred with 304 episodes of LOC (80%). Each veteran with LOC had at least one episode of LOC associated with an explosion. Factors contributing to combat mTBI were improvised explosive device—261, MVA—197, rocket-propelled grenade—52, artillery/mortar—32, bomb—20, and blunt trauma not associated with explosion or MVA—10. Combat mTBI could have several contributing factors. Explosions were often associated with an MVA. Five veterans reported one LOC in a non-combat setting caused by fall, fight, MVA, sports injury and striking a doorframe. Veterans also experienced episodes of AOC without LOC (only AOC).

The presence of an ND (including or excluding veterans whose only ND was impaired olfaction), the presence of PTSD, MOCA, PCL-M and olfaction scores were related to the number of episodes of LOC (table 2, figure 2). The mean MOCA score for one episode of combat-acquired LOC was 26.1±0.34 (n=34) and 25.3±0.36 for two episodes of LOC (p<0.05). Veterans with five or more episodes of LOC had mean MOCA scores of 24.2±0.41 (p<0.05 compared with two episodes of LOC). In contrast, the strengths of associations were weakened by considering mTBI episodes with only AOC. Associations of episodes of LOC + only AOC episodes were ND—0.131, PTSD—0.262, and MOCA—0.085 (all p<0.001). There were no associations of NDs, PTSD or MOCA scores with episodes of only AOC.

For veterans with PTSD, MOCA scores correlated inversely with PTSD severity measured with PCL-M scores (table 2, figure 3A). However, there was no correlation between MOCA and olfaction scores for veterans with an ND (table 2, figure 3B) or veterans with normal olfaction (data not shown). For veterans with PTSD and impaired olfaction, PCL-M scores were not correlated with olfaction scores (table 2, figure 4).

We compared OIF/OEF veterans with a group of 21 veterans who sustained mTBI with LOC in a civilian setting to evaluate the contribution of a combat setting (table 1). Neither group reported episodes of TBI before military service. Veterans with civilian mTBI reported no TBI during military service. All veterans with civilian mTBI had one episode of LOC. Intervals from the last TBI differed. Veterans with combat TBI were seen 122.6±4.4 weeks after the last TBI (range 40–212 weeks). This time reflected the time OIF/OEF veterans spent in the military before they were discharged and the time it took for the OIF/OEF veterans to obtain care through the CVAMC. We evaluated veterans with civilian TBI 8.38±0.53 weeks (range 4–12 weeks, p<0.001) after mTBI. Veterans with civilian mTBI had fewer NDs, lower frequency of PTSD and higher MOCA scores compared with those with combat mTBI (table 1). However, when veterans with civilian mTBI were compared with the 34 veterans who had one episode of combat mTBI, the two groups had similar frequencies of NDs of 4/34 (11.8%) for combat mTBI and 2/21 (9.5%, p-NS) for civilian mTBI. The two veterans with civilian mTBI and initial NDs did not have

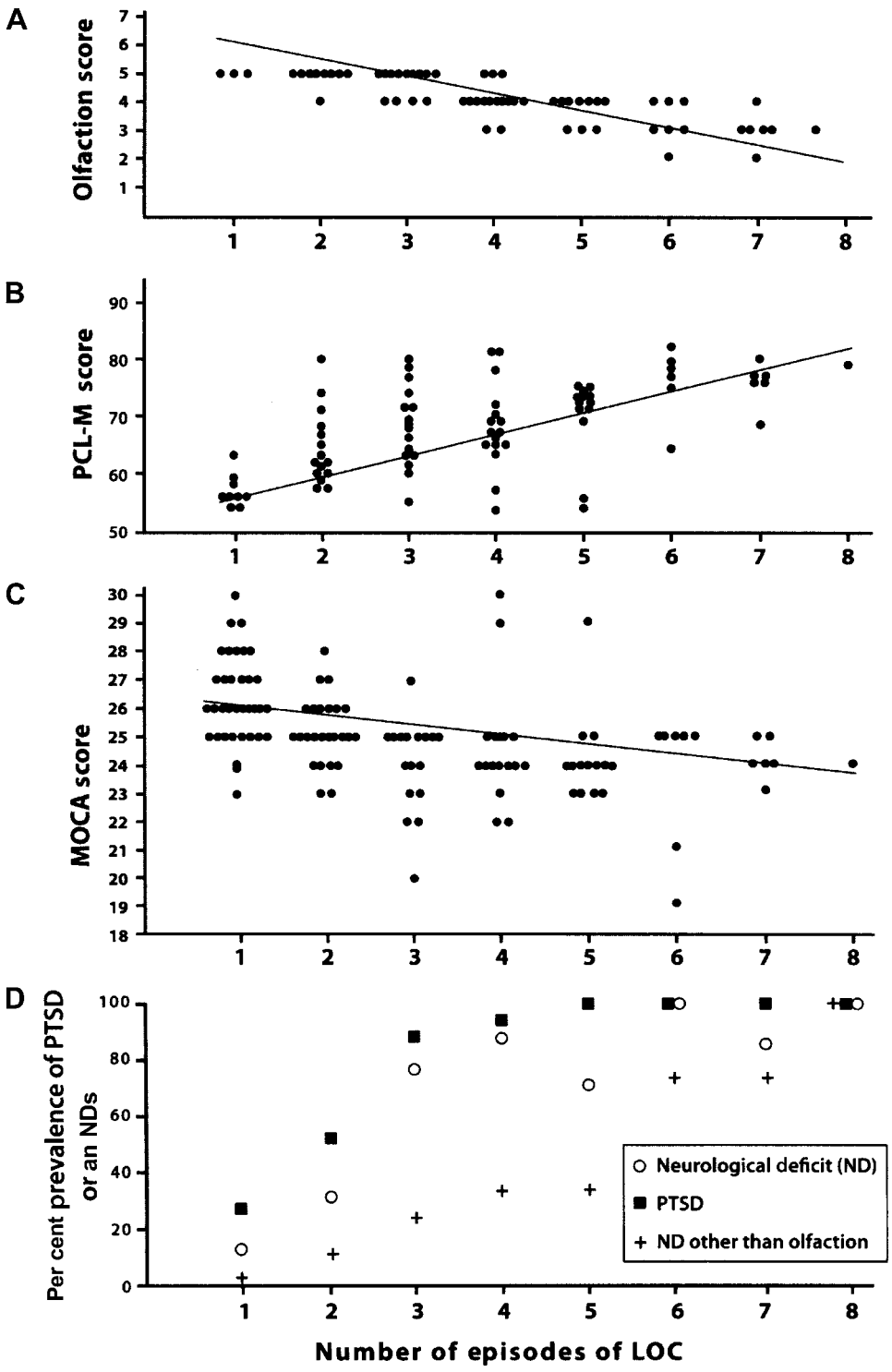

Figure 2 Effect of number of episodes of loss of consciousness (LOC) on outcomes for veterans with combat-acquired mild traumatic brain injury: (A) olfaction scores, (B) post-traumatic stress disorder (PTSD) severity as measured by the PCL-M score, (C) score on the Montreal Cognitive Assessment (MOCA) Test and (D) the prevalence of abnormalities on neurological examination (unfilled circles) or PTSD (filled squares). The correlation coefficients for the association between the number of episodes of LOC and the olfaction scores, PCL-M scores and MOCA score are shown in table 2. The straight lines in A, B and C correspond to Kendall's rank correlation analysis coefficients in table 2.

any NDs when re-examined 2 years later, an interval between TBI and evaluation comparable to the interval for combat mTBI. Due to the small sizes of the groups of veterans with mTBI and one episode of LOC, the ND prevalence values remained not significantly different. MOCA scores for veterans with civilian mTBI (table 1) were higher than for veterans with one episode of combat-associated LOC, 26.1±0.34, $p<0.001$. PTSD was more common for combat veterans with one episode of LOC (32.4% vs 4.8%, $p=0.0194$).

DISCUSSION

The data provided clear answers to the research questions: (1) the most frequent ND recognised was impaired olfaction that was discovered using quantitative olfactory testing and (2) there were definite associations between the number of episodes of mTBI with LOC and presence of NDs (both olfaction and NDs other than impaired olfaction) as well as an increase in the likelihood than a veteran would have PTSD with increased number of episodes of mTBI with LOC (figure 2). In

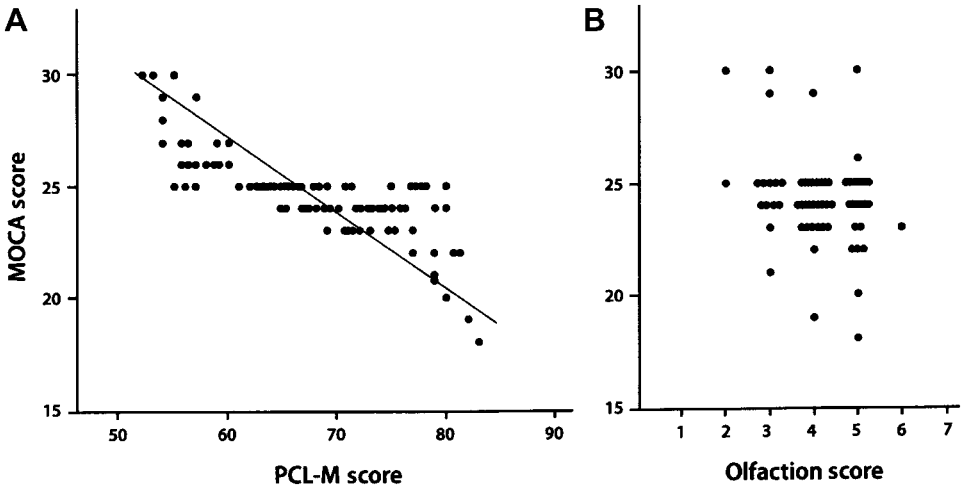

Figure 3 Association of the scores on the Montreal Cognitive Assessment (MOCA) Test with (A) post-traumatic stress disorder (PTSD) severity as measured by the PCL-M score for veterans with PTSD or (B) olfaction scores for veterans with neurological deficits including impaired olfaction. The correlation coefficients for the association between the MOCA scores and the PCL-M scores are shown in table 2. There was no association between MOCA scores and olfaction scores. The straight line in A corresponds to Kendall's rank correlation analysis coefficient in table 2.

addition, PCL-M scores, extent of olfactory impairment and reduction in MOCA scores increased with the number of episodes of LOC (figure 2). The most frequently recognised ND was impaired olfaction followed by impaired balance and abnormal saccades. Testing for olfaction using a 'scratch and sniff' instrument is easy to do in a clinic setting, has been validated for different subject groups and is amenable to a variety of settings including a combat environment.[14 15] We advocate incorporating olfaction testing into neurological examinations for TBI. Among the items in the 50 element neurological examination, the other elements, aside from olfaction, that indicated neurological dysfunction were the Romberg test, observation of saccades, asymmetric arm rolling/arm drift and consistent unilateral sensory extinction on simultaneous light touch stimulation of both upper extremities. About 40% of civilians with TBI have impaired balance[31] or impaired eye movements.[32] However, specialised testing environments are needed to detect the subtle changes in balance or eye movements produced by mTBI. These assessments are not done in a clinic setting. Olfactory testing is the most sensitive indicator of persisting injury following TBI that can be done in a clinic setting and is a good test for remote TBI because olfaction usually does not recover after TBI.[33]

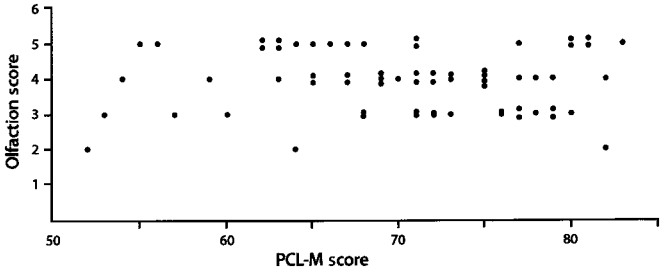

Figure 4 Association of the PCL-M and olfaction test scores for veterans with both NDs and post-traumatic stress disorder. The correlation coefficient for the association between the PCL-M scores and olfaction scores is shown in table 2. There was no significant association between PCL-M scores and olfaction scores.

We found the strongest associations between outcomes (NDs, PTSD and MOCA scores) and episodes of LOC. Veterans who experienced episodes of LOC had MOCA scores that were mildly reduced compared with those who did not experience episodes of LOC. The absolute differences in MOCA scores between different groupings of the veterans in this study were small, even though the differences may have been statistically significant. The high frequency of episodes of LOC associated with a blast prevented us from being able to discern differences between episodes of LOC associated with explosions and episodes of LOC not associated with explosions. All the veterans who had an episode of LOC had at least one episode of LOC associated with an explosion. When episodes of AOC as well as LOC were considered, the correlations were weaker and there were no correlations for episodes of AOC alone. We could not distinguish prevalence differences for NDs following civilian versus combat mTBI, but the numbers of veterans with one episode of LOC were small.

Several biases may have influenced this study. Episodes of TBI were historical. In some instances, veterans may have underestimated the duration of LOC so that some episodes of mTBI may have really been episodes of moderate TBI. Neurological examinations were not blinded. However, the olfaction test and the MOCA are objective tests that reduce the likelihood that RLR influenced veterans' performance. Due to the nature of the armed conflicts in the Middle East with repeated deployments for US combat troops and because episodes of mTBI were not likely to remove one from combat responsibilities, there could be a long time between the last episode of mTBI and VA assessment. This was not a random sample of veterans who sustained mTBI in OIF/OEF. Veterans who sustained mTBI without persisting problems would be less likely to seek treatment from the CVAMC, and veterans who had

complaints that might be attributed to a prior mTBI might misremember that an episode of trauma included mTBI when there was no TBI. The associations of NDs with episodes of mTBI suggest that the recalled episodes of mTBI were associated with cerebral injury. There were relatively few subjects in the comparison group of combat veterans who had mTBI without LOC. The size of this group was not representative of the expected fraction of combatants with mTBI without LOC. In two studies of military personnel who returned from deployment in Iraq or Afghanistan, between 26% and 32% of those who reported an episode of TBI reported having LOC.[4 34] However, the comparison groups were only used for the data shown in table 1. The data presented in the other table and figures do not involve the comparison groups. The presence of combat veterans up to 62 years of age may be due to two factors: (1) the delay between end of military service and enrolment for VHA care and (2) that 63% of those with LOC were National Guard or Reservists.

The MOCA is a cognitive screening test. Performance on the MOCA decreases with age and extent of education. The subjects in this study all had at least 12 years of formal education and were <65 years of age so that age would not be expected to have had a prominent effect on their MOCA performance.[17] As a cognitive function test, the MOCA is not as sensitive as detailed intelligence testing, but detailed intelligence testing would have taken longer times to administer. The MOCA has been used as a cognitive screening test for neurological disorders such as Parkinson's disease and stroke, and the MOCA is more sensitive than some other cognitive screening tests such as the Mini-Mental State Examination.[35 36]

Veterans with combat mTBI frequently complain of impaired cognition.[8] Did PTSD or NDs have the strongest influence on veterans' performance? PCL-M scores correlated with cognitive performance on the MOCA. Our data indicating that PTSD severity influenced cognitive performance is consistent with prior suggestions that PTSD influenced post-deployment symptoms including poor cognition.[4] The lack of association between MOCA and olfaction scores may indicate that the MOCA test is not sensitive to damage to orbital frontal cortex associated with impaired olfaction.[37] We found that deployment duration and the number of deployments were similar for veterans who did or did not suffer NDs and PTSD, which argues against NDs or PTSD resulting from factors that may be related to deployment durations such as exposure to a possible Middle East pathogen.

Was impaired olfaction caused by mTBI or other factors? Olfactory function can be impaired by smoking, sinus disease and inhalation of irritants.[29 30 38] We found no increase in smoking prevalence among veterans with impaired olfaction or differences in the history or presence of sinus disease. Exposure to pollutants and smoke, which may be present in a combat environment, produces ~12% decrease in olfaction test scores,[38] which would not explain our findings. PTSD does not compromise olfaction,[39] and we found that olfactory impairment did not correlate with PTSD severity. Therefore, we believe that reduced olfaction scores were likely due to repeated episodes of mTBI.

Quantitative tests of olfaction have not been used previously in studies of combat TBI. In one civilian study of mTBI, 22% of subjects had hyposmia and 4% had anosmia after one mTBI.[40] We found that 12% of veterans with combat mTBI and one episode of LOC had hyposmia. Civilian subjects may have had a higher prevalence of impaired olfaction because they were evaluated sooner. Injured olfactory nerve fibres can recover over time leading to recovery of olfaction during the first year after TBI.[41] Consequently, the veterans that we evaluated who had impaired olfaction, likely had permanent olfaction impairments. These olfaction impairments were usually not recognised by the veterans.

We believe that the olfaction deficits did not result in any functional limitations. The importance of the olfaction deficits was that they were markers of cerebral injury, specifically frontal lobe injury. The following text describes the relationships between TBI and impaired olfaction and how cerebral damage including injury to the ventromedial frontal lobes can enhance the likelihood that a psychologically traumatic event leads to the genesis of PTSD.

TBI usually impairs olfaction by shearing the olfactory nerves traversing the cribiform plate, bruising the orbital frontal cortex or both.[37] A study of US military personnel who sustained an episode of combat TBI, predominantly mTBI, in OIF/OEF found that 29% of subjects had white matter lesions in two or more areas of interest.[42] The areas of injury were orbital frontal cortex, cingulum and middle cerebellar peduncles. The finding of orbital frontal cortex injury associated with combat mTBI provides a structural cerebral correlation for our observation of impaired olfaction.

Civilian TBI studies indicate that neurological dysfunction correlates with the number of TBI events.[43 44] Recovery from mTBI is slower following repeated mTBIs.[45] Repeated sports concussions compromise cerebral electrical activity and metabolism.[46 47] Dementia and cerebral degeneration may be delayed consequences of repeated concussions.[48 49] Our observation that ND prevalence increased with combat mTBI episodes is consistent with observations from civilian concussions.

The increase in PTSD prevalence that we observed with LOC episodes may be due to several factors. The events causing LOC may have produced sufficient psychological trauma to induce PTSD. The presence of mTBI may have increased the likelihood that a psychologically traumatic event resulted in PTSD.[50] A study of the development of anxiety disorders in children following TBI found that 8.5% of children developed anxiety disorders, usually PTSD, within 6 months of the

TBI.[51] Children with mTBI had the greatest likelihood of developing PTSD. An Australian study of civilian trauma reported that the prevalence of PTSD following mTBI was 6%, which was about 1.9-fold higher than following trauma without TBI.[52] PTSD and mTBI are associated in combat personnel. About 40% of military personnel and veterans with combat-acquired mTBI have PTSD.[4 8] Among soldiers recently deployed in Iraq who experienced an episode of LOC due to mTBI, 44% had PTSD compared with 16% for soldiers with other injuries and 9% for uninjured soldiers.[4]

'Data suggest that PTSD is associated with over activation of the amygdala due to a lack of inhibitory control by ventromedial prefrontal cortex, as well as deficient hippocampal function.'[53] The areas of brain injury identified by functional imaging in PTSD including ventromedial frontal lobes and medial temporal lobes[54 55] are included within the areas damaged in mTBI.[42 56–58]

In this study, impaired olfaction was the most frequently recognised ND. To the extent that impaired olfaction is a marker for injury to orbital frontal cortex, impaired olfaction may be a flag for a cerebral injury that can facilitate the development of PTSD. The association of impaired olfaction with the presence of PTSD and PTSD severity is consistent with impaired olfaction being a marker for damage to orbital frontal cortex with reduced inhibition of the amygdala enabling anxiety and exaggerated fear responses.[53]

Pre-existing subtle ('soft') ND may increase the risk of developing PTSD.[59] The 45 neurological soft signs assessed in Vietnam veterans were similar to the 50 items in the neurological examinations performed in this study but did not include olfaction testing. In studies of monozygotic twins where one twin was in combat and the other not, among twins pairs where one had combat-associated PTSD, both twins had a higher prevalence of neurological soft signs[59] or grey matter abnormalities in the right hippocampus, pregenual anterior cingulate cortex and left and right insular cortex[60] than the twins where the combat-exposed twin did not have PTSD. The twin studies suggested that subtle genetically based NDs can potentiate the genesis of PTSD. This is, however, distinct from the findings of the Vietnam Head Injury Program (VHIP)[53] where veterans with combat penetrating TBIs were classified based on lesion location. The prevalence of PTSD was compared across groups. Patients with amygdala or ventromedial frontal injuries had reduced prevalence of PTSD. The apparent contradiction between the twins and VHIP studies may be due in part to differences in the severity of the injuries. Subjects in the twin studies had subtle performance and imaging deficits compared with the penetrating injuries in the VHIP study. Mild injury may potentiate PTSD genesis by slightly disrupting normal interactions among the amygdala, ventromedial frontal cortex and hippocampus, whereas more severe injury may prevent "the 'super-normal' levels of fear/anxiety that define PTSD."[53] In childhood TBI, development of PTSD and other anxiety disorders correlated with MRI-identified damage to the superior frontal gyrus, anterior frontal white matter and orbital frontal cortex.[51] Overall, the risk of an individual with combat TBI developing PTSD may be higher for mTBI compared with severe TBI.[61] Children with mTBI had a greater likelihood of developing PTSD than children who had severe TBI.[51] In addition, penetrating injuries may have been more focal and less likely to have the more diffuse axonal effects of closed head injury. We found that PTSD severity was not associated with the severity of olfaction impairment. Perhaps the presence of injury to orbital cortex predisposes to PTSD, but severity of cortex injury is not the primary factor controlling PTSD severity. Our observation that the severity of olfaction impairment was related to the number of LOC events suggests that impaired olfaction was related to combat mTBI rather than being pre-existing deficits.

Several factors can enhance or reduce the likelihood that a psychologically traumatic event results in development of anxiety disorders including PTSD. For example, psychological resiliency, a supportive social environment and higher levels of intelligence and education may reduce the likelihood of an individual developing PTSD.[22 62] This study suggests that mTBI in a combat setting may enhance the likelihood of an individual developing PTSD. Additional studies are needed to support or refute the suggestion from this study that mTBI increases the likelihood that combat trauma leads to PTSD.

There is a tendency to attribute physical symptoms after deployment to PTSD rather than to mTBI.[4] Future studies of combat TBI will determine the extent to which our findings of increased prevalence of PTSD and NDs with episodes of LOC generalise to other populations of military personnel and in other settings. Given the results detailed in this study suggesting a relationship between mTBI and PTSD, perhaps the focus of future studies should shift from ascribing cognitive deficits and physical symptoms to one diagnosis versus another to understanding the impact of repeated combat mTBI on development of PTSD.

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Contributors RLR examined the subjects, collected data, did data analysis and wrote the manuscript. RGR II edited the manuscript, assisted with data interpretation and wrote portions of the discussion. X-FW did the statistical analysis and edited the portions of the manuscript related to statistical

analysis. TP examined subjects and edited the manuscript. SSR examined subjects, assisted with study design and edited the manuscript.

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Competing interests There were no other actual or potential conflicts of interest for the authors that could have inappropriately influenced the present work. Subjects and their medical records were treated in accordance with internal review board approved policies and procedures. Standard professional and ethical guidelines were upheld during the research study and manuscript preparation. The views expressed in this article do not necessarily reflect those of the Veterans Health Administration of the Department of Veterans Affairs of the USA or the USA government.

Ethics approval Ethical approval was provided by Institutional Review Board of the Cleveland VA Medical Center.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement The data used in this study are available in the form of a subject de-identified spreadsheet that can be obtained by a written request to RLR, robert.ruff1@va.gov.

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Appendix 1 : Elements of neurological examination (web access only)

Exam Elements	Normal	Abnormal
Cranial Nerve Function (I-VII, IX-XII)		
I- Olfaction		
age <55 years	≥7/12 on BSIT-12	<7/12 on BSIT-12
age ≥55 years	≥5/12 on BSIT-12	<5/12 on BSIT-12
II- Confrontation Visual Fields		
III,IV,VI – Eye Movements		
Saccades		
Vertical		
Horizontal		
Smooth Pursuit		
Vertical		
Horizontal		
V – Facial Sensation		
Upper Face		
Middle Face		
Lower Face		
Jaw Opening Symmetric		
VII - Symmetric Facial Movement		
Eyelid closure		
Pucker cheeks		
Smile		
IX, X – Pharyngeal Function		
Symmetric gag reflex		
Symmetric soft palate elevation		
XI – Sternomastoid Function		
Symmetric mass		
Symmetric force		
XII – Tongue movement symmetric		
Motor Function		
Bulk symmetric		
Tone symmetric upper extremity		
Tone symmetric lower extremity		
Normal Strength left upper extremity		
Normal Strength right upper extremity		
Normal Strength left lower extremity		
Normal Strength right lower extremity		
Upper Extremity Drift	Absent	Present
Arm Rolling	Symmetric	One hand orbits the other
Sensation		
Normal to pin left upper extremity		
Normal to pin right upper extremity		
Normal to pin left lower extremity		
Normal to pin right lower extremity		
Normal to pin left upper extremity		
Normal to pin right upper extremity		
Normal to pin left lower extremity		
Normal to pin right lower extremity		
Extinction on double simultaneous Stimulation	Absent	Present
Upper extremity topognosia	Normal	Deficient

Exam Elements (continued)	Normal	Abnormal
Coordination Testing		
Finger to nose	Normal	Asymmetric, tremor
Heel to shin	Normal	Asymmetric, tremor
Upper extremity rapid alternating movements	Normal	Impaired
Reflex Testing		
Symmetric biceps reflex		
Symmetric brachioradialis reflex		
Symmetric triceps reflex		
Symmetric knee jerk		
Symmetric ankle jerk		
Babinski sign	Toes downgoing	Upgoing toe
Gait Testing		
Regular gait		
Heel walking		
Toe walking		
Tandem walking		
Romberg test		

Appendix 2: Number OIF/OEF veterans with episodes of LOC due to combat mTBI, non-combat mTBI arranged according to the total number of episodes of LOC reported.

	Number of Veterans with a Specific Total Number of Episodes of LOC (combat + non-combat)							
Total Number of Episodes of LOC	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Number of Veterans Who Only Had Combat mTBI	34	29	16	15	12	7	7	1
Veterans who had 1 episode of non-combat mTBI	0	0	1	2	2	0	0	0
Number of veterans for each number of episodes of LOC	34	29	17	17	14	7	7	1

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In Reply Refer To: 541/

February 19, 2012

BMJ Open Editorial Office:

We would like to submit a second revision of the manuscript entitled, “A Case-Control Study Examining Whether Neurological Deficits and PTSD in Combat Veterans Are Related to Episodes of Mild TBI”. All of the authors contributed to the revision and accepted the revised manuscript. The manuscript was extensively changed as detailed below in the response to the reviewer. As before, the appendices are for online publication.

Sincerely,

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The specific responses to the questions raised by Dr. Schwab are detailed in the following paragraphs.

Dr. Schwab's comments are indicted in ***as numbered bolded and italicized text.*** Portions of the R2 manuscript are included to demonstrate how we responded to the questions. The portions of the text that were changed from the first revision are shown in yellow highlighted text.

The excerpted text segments from the R2 manuscript do not contain the citation numbers. We developed the responses to Dr. Schwab's comments in parallel to revising the manuscript. The citations for the manuscript are entered using a bibliography generating program. It was not practical to format the text that is cited below to include the appropriate citation numbers. One can refer to the highlighted version of the revised manuscript to find the appropriate citation numbers.

In response to Dr. Schwab's request, we added a figure showing the steps in getting the study group from the original sample of OIF/OEF veterans. We also added references suggested by Dr. Schwab. The revised set of figures is submitted in ".tif" format at figure resolutions of 300 and 600 dpi. We have 1200 dpi versions of each figure, if they are needed. We revised the Strobe Checklist.

1. Research question is not clearly defined - reads like an exploratory analysis. If so, needs to be stated.
In response to this comment from Dr. Schwab, the primary research questions have been clearly stated in the introduction:

"In this case controlled observational study, we screened 2091 OIF/OEF veterans and identified 126 veterans who had ≥ 1 episode of combat mTBI associated with loss of consciousness (LOC). The research questions we examined were: 1) what are the most frequently recognized NDs that can be identified during an examination performed in a clinic setting? 2) Do associations exist between the episodes of TBI and NDs or PTSD?"

2. Study design: since the research question is not clear, it follows that the study design was not tailored to the question.
Dr. Schwab is absolutely correct that this was a case controlled observational study. We used comparison groups of veterans who underwent the same evaluations who did not have LOC or who had mTBI with LOC in a civilian setting. The introduction was revised to more clearly indicate the study design:

We evaluated veterans for NDs and PTSD and correlated outcomes with LOC episodes. We had two comparison groups. To evaluate whether episodes of mTBI with LOC differed from mTBI without LOC, we compared the findings in combat veterans who experienced mTBI episodes with LOC to combat veterans who did not have any LOC episodes. To consider if a combat setting influenced the likelihood of a veteran

having residual NDs, we compared the findings in combat veterans who experienced mTBI episodes with LOC to veterans who suffered mTBI with LOC as civilians. The veterans in the comparison groups had the same testing as the veterans who had combat mTBI with LOC, which led to the smaller sizes of the comparison groups relative to the study group.

3. The VA patients are likely not receiving care for their mTBI alone - the report needs to describe the other health issues/injuries the subjects have - that might be useful for interpretation. Also, it is important to state clearly (other than just describing the screening tool) that to be considered screen positive in the VA, individuals must be currently symptomatic with symptoms associated with mTBI. Most mTBI patients' symptoms resolve much sooner than 2 years out - so the subjects likely have other conditions causing continued symptoms, or may be atypical of OIF/OEF mTBI individuals.

The Methods section was revised in accord with this comment from Dr. Schwab.

"Subject Selection - OIF/OEF veterans: The OIF/OEF veterans were individuals who sought care from VHA often for issues not related to TBI such as treatment of musculoskeletal pain or choosing VHA to be their personal health resource. In addition, many individuals had mental health issues such as depression and PTSD. OIF/OEF veterans were screened for TBI using a three level sequential process. The first screening step was a 4 question screening tool that was administered to all OIF/OEF veterans treated by VHA.{Donnelly, 2011 #3162} For those who confirm OEF or OIF deployment and do not have a prior diagnosis of TBI, the instrument proceeds using four sequential question sets. The initial screen is negative if a person responds negatively to any question set. If the veteran affirms ≥ 1 possible answer in each section, the screen is positive. The four sections are: (a) events that could heighten the risk of TBI such as explosion exposure, (b) immediate symptoms following the event including LOC, AOC or PTA, (c) new or worsening symptoms following the event and (d) current symptoms that are consistent with TBI. The natural history of mTBI is that most individuals with civilian mTBI not associated with an explosion have resolution of symptoms within 6 months. The recovery pattern of combat mTBI associated with an explosion is that a greater fraction of individuals can have persisting post-concussion symptoms following mTBI; however, these individuals also have PTSD that is likely contributing to the persistence of symptoms. The symptoms in the screen included alterations in cognition, behavior, motor or sensory function, balance or coordination and the presence of pain including headache."

4. The researchers count the number of mTBI with LOC - but do not state whether or not their stringent criteria of witnessed LOC etc was true for multiple LOC events.

The Methods section indicates that the criteria for LOC applied for each episode.

"For each episode, LOC referred to a period when someone at the trauma scene observed the veteran to be unresponsive or the veteran did not move when prompted or nudged. If there were no observers, veterans could indicate an episode of LOC by stating that they clearly aroused or "woke-up" following head trauma."

(5) 4. Representative nature of sample: I understand the way the sample was gathered - but the very small numbere of TBI with no loss of consciousness is not understandable, given the existing literature. Age range includes individuals older than I would expect from the population - needs explanation. Flow diagram with missings included would help.

We added a flow diagram (figure 1) of the sequential process of subject selection.

The small number of combat veterans in the comparison group of reflected the number of veterans without LOC who had passed through the screening process. The Methods section states:
"The 155 veterans evaluated by RLR were divided into two groups. One group contained 126 veterans who had ≥ 1 episode of combat mTBI with LOC. The second group contained 21 combat veterans who did not sustain LOC: 11 veterans with mTBI in a combat setting, 5 veterans who had mTBI in a non-combat setting and 5 veterans who did not have a definite episode of TBI. In the last sub-group of 5 veterans, each veteran had at least one episode of exposure to an explosion that was associated with a behavioral change that RLR interpreted as possible but not definite episodes of AOC. The episodes in these 5 veterans may have been changes in arousal or emotion associated with combat rather than episodes of AOC. Thus in this group of 21 veterans, 16 had episodes of mTBI associated with AOC and 5 had episodes that may have been mTBI. We excluded 8 veterans who had moderate or penetrating TBI. The size of the comparison group of combat veterans with mTBI without LOC reflects the small fraction of veterans who did not have LOC among the 155 veterans examined by RLR. The 155 veterans examined by RLR had undergone two prior screening evaluations that indicated the veterans had mTBI with persisting residual symptoms such as headache. Seventy-nine/126 veterans (62.7%) who had combat mTBI with LOC and 12/21 (57.1%) who did not have LOC were National Guard or Reservists."

The Discussion section now points out that the size of the comparison group of veterans who had combat mTBI without LOC was small and not representative of the expected fraction of veterans who had mTBI without LOC:
"There were relatively few subjects in the comparison group of combat veterans who had mTBI without LOC. The size of this group was not representative of the expected fraction of combatants with mTBI without LOC. In two studies of military personnel who returned from deployment in Iraq or Afghanistan, between 26% and 32% of those who reported an episode of TBI reported having LOC. However, the comparison groups were only used for the data shown in Table 1. The data presented in the other table and figures do not involve the comparison groups."

The older age of some of the study subjects is addressed in the Discussion:
"The presence of combat veterans up to 62 years of age may be due to two factors: 1) the delay between end of military service and enrollment for VHA care and 2) that 63% of those with LOC were National Guard or Reservists."

6. Main outcome measure: Not clear which measure was primary.

The Methods section now states:
"The primary outcome measures were presence of NDs and presence of PTSD. The secondary outcome measures were olfaction scores, PCL-M scores and MOCA scores."

(7.) 11. There are appropriate references that need to be included (recent lit), including a large critical study of the MoCA..
We removed the suggestion of there being a lower normal score of 26 for the subjects in this study. The largest issues for MOCA scores apply to subjects older than 65 years of age and who have less than 12 years of education. The educational and age range for our subjects were outside of the aforementioned ranges. We included citations to three newer references related to the MOCA. Of note, the Rossetti article was published after our original manuscript to BMJ Open was submitted.
1. Hoops S, Nazem S, Siderowf AD, Duda JE, Xie SX, Stern MB, et al. Validity of the MoCA and MMSE in the detection of MCI and dementia in Parkinson disease. *Neurology* 2009;73:1738-1745.

2. Pendlebury ST, Cuthbertson FC, Welch SJ, Mehta Z, Rothwell PM. Underestimation of cognitive impairment by Mini-Mental State Examination versus the Montreal Cognitive Assessment in patients with transient ischemic attack and stroke: a population-based study. *Stroke* 2010;41:1290-1293.

3. Rossetti HC, Lacritz LH, Cullum CM, Weiner MF. Normative data for the Montreal Cognitive Assessment (MoCA) in a population-based sample. *Neurology* 2011;77:1272–1275.

We added a paragraph about the MOCA in the Discussion section:
"The MOCA is a cognitive screening test. Performance on the MOCA decreases with age and extent of education. The subjects in this study all had at least 12 years of formal education and were less than 65 years of age so that age would not be expected to have a prominent effect on their performance. As a cognitive function test the MOCA is not as sensitive as detailed intelligence testing, but detailed intelligence testing would have taken longer times to administer. The MOCA has been used as a cognitive screening test for neurological disorders such as Parkinson's disease and stroke and the MOCA is more sensitive than some other cognitive screening tests such as the Mini-Mental State Examination."

8. Though not on the list: the paper mentions Bonferroni corrections were used However, need to explain how the adjustment was made. Table 2 presumably used, but need to describe the correction for the p value. It is surprising these small differences remained significant after corrction.

We clarified the use of the Bonferroni corrections in the Methods section:

The Bonferroni method was used to correct for multiple comparisons. The Bonferroni p-value ($p_{Bonferroni}$) adjusts the raw p-value (p_{raw}) for the number of times that a hypothesis is tested (number of comparisons = m), $p_{Bonferroni} = m \bullet p_{raw}$. If the adjusted p-value exceeds 1, it is set to 1. The Bonferroni test is conservative but always controls the familywise error rate. The probability values shown in Tables 1 and 2 were corrected using the Bonferroni method.

9. I will add that the finding of olfaction deficits (generally not recognized by subjects) is potentially interesting, relatively unique, and important for future investigations. The authors' interpretation of the relevance of their finding is not as strong as could be - do they see it primarily as a marker of frontal lobe injury, etc? Does olfaction have relevance as a correlate of other problems/issues?

We state that olfaction testing is an important evaluation element early in the Discussion section:

"The most frequently recognized ND was impaired olfaction followed by impaired balance and abnormal saccades. Testing for olfaction using a "scratch and sniff" instrument is easy to do in a clinic setting, has been validated for different subject groups and is amenable to a variety of settings including a combat environment. We advocate incorporating olfaction testing into neurological examinations for TBI."

We revised the Discussion section to indicate more clearly that we feel that impaired olfaction is a marker of frontal lobe injury and that frontal lobe injury may enhance the likelihood of PTSD genesis following a psychologically traumatic event.

"We believe that the olfaction deficits did not result in any functional limitations. The importance of the olfaction deficits was that they were markers of cerebral injury, specifically frontal lobe injury. The following text describes the relationships between TBI and impaired olfaction and how cerebral damage including injury to the ventromedial frontal lobes can enhance the likelihood that a psychologically traumatic event leads to the genesis of PTSD."

10. Second, other NDs are not analyzed well - might be useful to at least look at "other NDs" with a bit more detail.

We expanded the description in the Results section of the NDs other than olfaction:

Neurological deficits were: reduced olfaction – 65, impaired balance – 14, abnormal eye movements – 13, motor asymmetry – 2 and sensory change – 2. Twenty-nine veterans had > 1 ND. Among the 65 veterans with NDs, 36 (55%) had only impaired olfaction. Impaired balance was detected using the Romberg test. The most frequently recognized abnormal eye movement was saccadic dysmetria (12 individuals), with one individual having asymmetric horizontal saccade velocity. Motor asymmetry was detected with arm-rolling and upper extremity drift that were both present in two

subjects. The two veterans with sensory changes had extinction on simultaneous stimulation.

The following highlighted text was added to the Discussion:
"Among the items in the 50 element neurological examination, the other elements, aside from olfaction, that indicated neurological dysfunction were the Romberg test, observation of saccades, asymmetric arm rolling/arm drift and consistent unilateral sensory extinction on simultaneous light touch stimulation of both upper extremities. About 40% of civilians with TBI have impaired balance or impaired eye movements. However specialized testing environments are needed to detect the subtle changes in balance or eye movements produced by mTBI. These assessments are not done in a clinic setting. Olfactory testing is the most sensitive indicator of persisting injury following TBI that can be done in a clinic setting and is a good test for remote TBI because olfaction usually does not recover after TBI."

11. Group 2: not clear the relevance of the group as constituted. If want sample of any screened positive patients without LOC, would seem to be missing cases. If want sample of MTBI patients without LOC would seem to need to remove suspect cases. Depends on purpose of this control group.
We wanted to compare mTBI with LOC to mTBI without LOC. In Table 1 we present data from both the group of 21 veterans who definitely and probably had mTBI without LOC and the group of 16 veterans who definitely had mTBI without LOC. The findings from the smaller group of 16 were similar to the group of 21. The Results section has the following text added:
"The comparison group of 16 veterans who had definite episodes of mTBI without LOC also had a lower frequency of PTSD and higher MOCA scores (Table 1). The olfaction scores of the group of 16 veterans were also higher than the scores of the veterans who had mTBI with LOC without a ND, 11.25 ± 0.11 ($p<0.01$)."

We point out in the Discussion that the comparison groups were used in only a small fraction of the data presented:
"However, the comparison groups were only used for the data shown in Table 1. The data presented in the other table and figures do not involve the comparison groups."

12. Measures: MoCA has been suggested by recent research to be a weak measure, and that may partly explain the unusual findings of continued cognitive issues in these mTBI patients (though other health issues/injuries may also explain).
We responded to issues related to the MOCA test above, in response to Dr.Schwab's 7th point.

13. PCL-M was used to develop quantitative scores. However, clinician confirmation of PTSD is alluded to - was the PCL-M used even with a negative clinician eval?

"Veterans who screened positive were assessed using a 17 item National Center for PTSD checklist for symptoms of military PTSD (PCL-M) and the veterans were referred for further evaluation by a mental health professional qualified to diagnose PTSD."

14. Interpretation of results fuzzy, and it is unusual to have so much research reviewed in the last sections of a research paper.
The article follows the Guidelines well - only problem area is developing reasonable conclusions from findings.

The Discussion section was extensively revised as discussed in response to prior points raised by Dr. Schwab. We hope that the revisions clear up some of the issues that were not clear.

15. I wonder if the researchers conducted additional analyses that are not reported just because of a lack of research objectives and the less than well organized presentation. Not a problem to have conducted additional analyses, but if the case need to explain is an exploratory study, etc.

Dr. Schwab appropriately sensed that our group had hoped to use the data described in this manuscript as the pilot data to provide a justification for a larger planned, controlled, blinded and externally funded research project. It has taken us longer that we had hoped to be able to progress through the process of developing a protocol. We are thankful that US troop involvement in Iraq and Afghanistan has been greatly reduced. The reduction in US combat troops in the Middle East combined with probably reduction in research funding makes it highly unlikely that we will be able to perform a blinded and controlled study of the impact of number of episode of LOC upon prevalence of PTSD and NDs.
We describe the study as "observational" in the Introduction and Methods sections.

16. The paper is in need of a clearer focus, and explanation of the very small sample size for the first control group. In addition, measurement issues are a problem (see Rossetti et al, Neurology 2011 re MoCA) that needs to be acknowledged. And, some helpful information is missing - such as verification of all episodes with LOC, etc. One gets the sense that this paper has been revised several times with extra paragraphs added in response to reviewers? At any rate, the report needs to be focused on the research questions (or alternatively described as an exploratory study) with more discussion of the interesting findings on olfaction.

We believe that the revisions made to the manuscript in response to Dr. Schwab's comments have provided a clearer focus to the manuscript and a better Discussion section. We addressed issues related to the MOCA in response to point #7 by Dr.Schwab.

STROBE Statement—Checklist of items that should be included in reports of ***case-control studies***

	Item No	Recommendation
Title and abstract Yes, reviewed	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale p6-7	2	Explain the scientific background and rationale for the investigation being reported
Objectives p.7	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design p.7-8	4	Present key elements of study design early in the paper
Setting p. 8-10	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants p.8-10	6	(*a*) Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls
		(*b*) For matched studies, give matching criteria and the number of controls per case
Variables p. 13-14	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement p.11-13	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias p. 20-21	9	Describe any efforts to address potential sources of bias
Study size p. 8-12	10	Explain how the study size was arrived at
Quantitative variables p. 13-14	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods p. 13-14	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how matching of cases and controls was addressed
		(*e*) Describe any sensitivity analyses
Results		
Participants p. 8-12	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data p. 14-15	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
Outcome data p.15-16	15*	Report numbers in each exposure category, or summary measures of exposure
Main results p. 14-18	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period

Other analyses p. 17-18	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results p.19	18	Summarise key results with reference to study objectives
Limitations p. 20-21	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation p. 21-26	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results p.26
Other information		
Funding p. 37-8	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.