PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (see an example) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below. Some articles will have been accepted based in part or entirely on reviews undertaken for other BMJ Group journals. These will be reproduced where possible.

ARTICLE DETAILS

| TITLE (PROVISIONAL) | A Case-Control Study Examining Whether Neurological Deficits and PTSD in Combat Veterans Are Related to Episodes of Mild TBI |
| AUTHOR(S)          | R.L. Ruff, R.G. Riechers II, Xiao-Feng Wang, T Piero N.P. and S.S. Ruff |

VERSION 1 - REVIEW

| REVIEWER | Geoffrey S. F. Ling, M.D., Ph.D., F.A.A.N. Colonel, Medical Corps, U.S. Army Professor and Interim Chair of Neurology Uniformed Services University of the Health Sciences USA |
| I have no competing interests and have nothing to disclose as it pertains to this topic. |
| REVIEW RETURNED | 07/09/2011 |

THE STUDY

The tables are appropriate and are supportive of the text conclusions. They are properly reported in the manuscript and do not raise questions about the work.

GENERAL COMMENTS

Was there any insights as to other mechanisms of injury? It is appreciated that 80% were blast but did the 20% "other mechanisms" have any influence on the results? Did the duration of LOC matter as this would suggest a more severe TBI than Grade 3 concussion?

| REVIEWER | Alan L. Peterson, PhD University of Texas Health Science Center at San Antonio |
| I have no competing or conflicts of interest. |
| REVIEW RETURNED | 01/10/2011 |

THE STUDY

The description of the second group of veterans is not clear. This group is often described as "veterans who did not suffer mTBI with LOC." Does this mean they did not suffer mTBI or LOC or that the suffered mTBI but did not have LOC?

The Abstract states, “…altered cognition following mTBI may increase the likelihood that a traumatic event results in PTSD.” This comment is not discussed in much detail in the manuscript. This line of discussion should be pursued in further detail, especially given that it is a main point in the abstract.

The Abstract does not mention the finding of the alteration in olfaction. This is a major finding of the study, and would likely
warrant mention in the abstract’s conclusion section.

REPORTING & ETHICS
The authors state the IRB approval was obtained, but they do not describe if and how informed consent was obtained.

GENERAL COMMENTS
This article describes a case control study which assessed the relationship between mild traumatic brain injury (mTBI), Posttraumatic Stress Disorder (PTSD) diagnosis, and neurological deficits in OIF/OEF veterans. For the purpose of this study, caseness (N=126) was defined as an OIF/OEF veteran who sustained mTBI with ≥ 1 episodes of loss of consciousness (LOC) in combat. Control groups where combat veterans who did not experience an LOC episode (N=21) and combat veterans who sustained mTBI with LOC as civilians (N=21). Consistent with previous findings, the authors reported that the prevalence of PTSD positively correlated with the number of mTBI with LOC combat injuries. They also found that neurological deficits, specifically impairment in olfaction, increased with number of LOC episodes. Notably, the authors did not find a significant difference in prevalence of neurological deficits for combat veterans who sustained one episode of LOC in a combat-related injury when compared to veterans whose injury was sustained as a civilian. The authors discuss possible explanations for their findings, and conclude that further research need be done to increase our understanding of the impact of repeated combat mTBI on development of PTSD.

ABSTRACT

The term “soldiers” appears to be used at times when referring to the broad group of military service members. If referring to members of the United States Army, or members of another country’s Army, this term is accurate. If referring to members of the armed services in general, it is not. Military personnel serving in the Marines, Navy, Air Force, or Coast Guard are not soldiers.

The composition of the second group of veterans is not clear in the abstract and throughout the manuscript. This group is often described as “veterans who did not suffer mTBI with LOC.” Does this mean they did not suffer mTBI or LOC or that the suffered mTBI but did not have LOC?

The Abstract conclusion states, “…altered cognition following mTBI may increase the likelihood that a traumatic event results in PTSD.” However, this comment is not discussed in much detail in the manuscript. This line of discussion should be pursued in further detail, especially given that it is a main point in the abstract.

The Abstract conclusion does not mention alteration in olfaction finding. This is a major finding of the study, and would likely warrant mention in the abstract’s conclusion section.

INTRODUCTION

Overall, very brief. Discussion of findings related to topic addressed in case control study could be expanded with relevant literature.

Page 6, Lines 18-19: It is recommended that the authors further research this statistic, as there is a wider range of reported injury than indicated here.

METHODS
The discrepant case vs. control group sample sizes is striking. Although this is not uncommon in case control studies, it would be helpful to discuss the rationale for this discrepancy in the methods section. A common initial reaction would be to assume that, due to the discrepancy, the result may over- or under-represent true group differences. Discussion of this issue would be important to the overall readability of the manuscript.

Page 7, Line 34: Description of the “TBI screening tool” is recommended.

Page 7, Line 51: Acronym “RLR” is first used, but not defined. I believe this is referring to the first author. If so, please state.

Veterans with civilian mTBI description would be helped by inclusion of greater definition of the time of injury. It states in the Discussion section that all injuries in this group were incurred post-deployment. This would be helpful information to include in the Methods section.

Page 9, “Neurological Examination”: Would recommend more thorough description of the methods used. Also, please explain why the MOCA was chosen as the cognitive assessment measure.

Page 9, Lines 25-32: this is a run-on sentence that should include a semicolon or be broken into two sentences.

Page 9, Description of PTSD assessment: What was initial 4-item screen? Was it the PC-PTSD? Please expand and reference, if appropriate. Also, the authors state that veterans received further evaluation by a mental health professional and were also administered the PCL-M. Was that the entirety of what was done by the mental health professional? Was there also a clinical interview (CAPS or PSS-I)? Clarification on this issue is recommended.

Page 9, Line 56: Lists PTSD and PCL-M scores as separate dependent variables. Of what does variable “PTSD” consist? Is it the presence or absence of a diagnosis of PTSD? Clarification on this issue is recommended.

RESULTS

Overall, the statistical analysis seemed appropriate.

Page 10, Lines 46-47: As presented here and throughout the manuscript, the authors refer to deployment length, but do not clarify the number of deployments. I was unclear as to whether the mean deployment lengths reported were for the deployment in which the injury occurred, or if it summed the length of all deployments of the veteran. Clarification is recommended.

Furthermore, it is recommended that mean number of deployments be reported here, as well.

Page 10, Line 56: Reference to PTSD – is this referring to number/severity of PTSD symptoms or to frequency of PTSD diagnosis in the population? Clarification is recommended.

Page 12, Line 10: Authors report 3.02 ± 0.20 episodes of LOC per veteran. A referral to Appendix 2 suggests that this is not a
representative description of the case group. May be better to describe range and mean, rather than ascribing a "per veteran" rate.

Page 12, Lines 39-47: Listed group mean MOCA scores show very small differences in scores between groups (mean MOCA score of 26.1 [1 episode LOC], 25.3 [2 episodes], and 24.2 [≥ 5 episodes]). Although these differences may be statistically significant, comments regarding the clinical significance should be included in the discussion section.

Authors often describe the case group without comparison to the control groups.

DISCUSSION

Case control studies are understood to be a less vigorous form of empirical science than randomized control trials; however, given the nature of the research topic, the chosen study method is very appropriate. However, this limits the authors' Discussion due to the fact that such a research approach can report correlation and not causation. Thus, it would have been helpful to a hear more about how the current study can be used to inform future research directions.

Would benefit from further discussion of the limitations of a possible self-selection bias. For example, veterans are often unaware of potential mTBI episode if not referred for further assessment. This does not preclude them having been injured by blast percussions without significant symptoms. Therefore, given that veterans are referred for further assessment in theater for a small number of the overall blasts to which they may be exposed, the veterans may be underreporting their injury history.

Overall impression of manuscript is that it does not read very well due to its abrupt nature. Would benefit from more explanation and description throughout. Perhaps if this is not possible due to page number limitations of the journal, the authors should consider reporting separately on the major findings of their study (i.e., Positive correlation between both PTSD and olfaction impairment and number of episodes of LOC).

Although an important contribution to an established research topic, the study seems to describe a previously well-observed phenomenon without significantly furthering our knowledge base about the phenomenon. At this point, may be more helpful for studies to begin to assess the mechanism of the correlation, rather than further describing the correlation itself.

FIGURES AND GRAPHS

No suggestions.

TABLES

Tables are somewhat difficult to read. Perhaps bolding to distinguish headings would be more reader-friendly.

REFERENCES

No suggestions.
SUPPLEMENTAL MATERIALS

No suggestions. Appropriate and raise no concerns.

VERSION 1 – AUTHOR RESPONSE

Dr. Ling’s Concerns
1. Were there any insights as to other mechanisms of injury? It is appreciated that 80% were blast but did the 20% “other mechanisms“ have any influence on the results?

Response
Unfortunately, the distribution of the mechanisms of injury among the military personnel in this study does not permit us to consider differences in the manifestations of mTBI associated with explosion vs. other mechanisms – usually head impact injury associated with a MVA. The first paragraph of the Discussion contains the following added text, “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 of the veterans who had an episode of LOC had at least one episode of LOC associated with an explosion.”

2. Did the duration of LOC matter as this would suggest a more severe TBI than Grade 3 concussion?

Response
Unfortunately, the veterans usually recalled the duration of LOC within a range of times. They could tell from the circumstances or from feedback from a comrade that they were unresponsive for less than 30 minutes, but they could not provide precise times. Hence we are really not able to do an analysis of the impact of duration of LOC on outcomes. Dr. Ling raises a good point that perhaps the duration of LOC may have been underestimated in some instances and we now point this out in the Discussion: “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.”

Dr. Peterson’s Concerns
1. The description of the second group of veterans is not clear. This group is often described as “veterans who did not suffer mTBI with LOC.” Does this mean they did not suffer mTBI or LOC or that the suffered mTBI but did not have LOC?

Response
The description of the group of combat veterans who had episodes or possible episodes of mTBI without LOC is better described in the Methods section. The text below was added to the Methods section.
“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 group of 5 veterans, each 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.”

2. The Abstract states, “…altered cognition following mTBI may increase the likelihood that a traumatic event results in PTSD.” This comment is not discussed in much detail in the manuscript.
This line of discussion should be pursued in further detail, especially given that it is a main point in the abstract.

Response
The review makes an excellent point. The abstract was reworded to state “altered cerebral functioning” rather than “altered cognition” to better fit with the arguments presented in the Discussion section. The end of the discussion now focuses on how frontal injury could predispose to the genesis of PTSD. The next to last paragraph of the Discussion states:

“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.(King, 1999 #3185; Peterson, 2011 #3184) This study suggests that the 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.”

3. The Abstract does not mention the finding of the alteration in olfaction. This is a major finding of the study, and would likely warrant mention in the abstract's conclusion section.

Response
The beginning of the Conclusion section of the abstract now states: “Impaired olfaction was the most frequently recognized NS.” The first paragraph of the Discussion now states:

“The most frequently recognized ND was impaired olfaction. 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.(Doty, 1996 #2635; Doty, 2001 #2598) We advocate incorporating olfaction testing into neurological examinations for TBI.”

4. The authors state the IRB approval was obtained, but they do not describe if and how informed consent was obtained.

Response
This point is clarified in the beginning of the Methods section:

“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 was 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 authorization; granted a waiver of informed consent and approved submission of the data in this manuscript for publication.”

5. The term “soldiers” appears to be used at times when referring to the broad group of military service members. If referring to members of the United States Army, or members of another country's Army, this term is accurate. If referring to members of the armed services in general, it is not. Military personnel serving in the Marines, Navy, Air Force, or Coast Guard are not soldiers.

Response
Dr. Peterson makes an excellent point. I went through the manuscript carefully to examine how military personnel are named. The term “soldier” is used only for veterans of the U.S. Army.

6. The composition of the second group of veterans is not clear in the abstract and throughout the
manuscript. This group is often described as “veterans who did not suffer mTBI with LOC.” Does this mean they did not suffer mTBI or LOC or that the suffered mTBI but did not have LOC?

Response
The Abstract was amended to state: “Control groups: 21 combat veterans who had definite or possible episodes of mTBI without LOC and 21 veterans who sustained mTBI with LOC as civilians. “

7. The Abstract conclusion states, “…altered cognition following mTBI may increase the likelihood that a traumatic event results in PTSD.” However, this comment is not discussed in much detail in the manuscript. This line of discussion should be pursued in further detail, especially given that it is a main point in the abstract.

Response
See the above response to issue #2 of Dr. Peterson.

8. The Abstract conclusion does not mention alteration in olfaction finding. This is a major finding of the study, and would likely warrant mention in the abstract’s conclusion section.

Response
See the above response to Dr. Peterson’s third issue.

9. Overall, very brief. Discussion of findings related to topic addressed in case control study could be expanded with relevant literature. Page 6, Lines 18-19: It is recommended that the authors further research this statistic, as there is a wider range of reported injury than indicated here.

Responses
The introduction was expanded in response to this comment:
When U.S. Army troops were evaluated after a deployment to Iraq, between 15% and 20% reported at least one episode of TBI, predominantly mTBI.(Hoge, 2008 #2693; Terrio, 2009 #2944; Theeler, 2010 #3111) In a study of U.S. National Guard soldiers who were deployed to Iraq, when queried one month before the end of a deployment, 9.2% of soldiers reported a mTBI during the deployment and 22.0% reported a mTBI during the deployment when queried one year later.(Polusny, 2011 #3177) 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.”(Polusny, 2011 #3177) 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.”(Polusny, 2011 #3177)

10. The discrepant case vs. control group sample sizes is striking. Although this is not uncommon in case control studies, it would be helpful to discuss the rationale for this discrepancy in the methods section. A common initial reaction would be to assume that, due to the discrepancy, the result may over- or under-represent true group differences. Discussion of this issue would be important to the overall readability of the manuscript.

Response
The Methods section was amended in response to this comment. The following text was added: “The relatively small size of the second group 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.”

11. Page 7, Line 34: Description of the “TBI screening tool” is recommended.

Response
The description of the 4 question TBI screen was expanded. The following text was added to the Methods section.
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 loss or altered consciousness or post traumatic amnesia, (c) new or worsening symptoms following the event and (d) current symptoms that are consistent with TBI. The symptoms in the screen included alterations in cognition, behavior, motor or sensory function, balance or coordination and the presence of pain including headache.

12. Page 7, Line 51: Acronym “RLR” is first used, but not defined. I believe this is referring to the first author. If so, please state.

Response
The Methods section was amended with the following text added, “The first author (RLR) . . .”

13. Veterans with civilian mTBI description would be helped by inclusion of greater definition of the time of injury. It states in the Discussion section that all injuries in this group were incurred post-deployment. This would be helpful information to include in the Methods section.

Response
The description of the civilian mTBI group in the Methods section was revised in accord with Dr. Peterson’s comment:
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.

14. Page 9, “Neurological Examination”: Would recommend more thorough description of the methods used. Also, please explain why the MOCA was the chosen as the cognitive assessment measure.

Response
The description of the physical examination was expanded in the Methods section:
“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.”

The following text was added related to why we used the MOCA, “We chose the Montreal Cognitive Assessment Test (MOCA) 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. {Nasreddine, 2005 #2763}”
15. Page 9, Lines 25-32: this is a run-on sentence that should include a semicolon or be broken into two sentences.

Response
This sentence was changed.

16. Page 9, Description of PTSD assessment: What was initial 4-item screen? Was it the PC-PTSD? Please expand and reference, if appropriate. Also, the authors state that veterans received further evaluation by a mental health professional and were also administered the PCL-M. Was that the entirety of what was done by the mental health professional? Was there also a clinical interview (CAPS or PSS-I)? Clarification on this issue is recommended.

Response
The Methods section was revised to more clearly state what was done. The following text was added:

“Every combat veteran was assessed for PTSD using the Primary Care PTSD Screen (PC-PTSD).{Prins, 2003 #3181} The initial screen had four questions about PTSD symptoms, if a veteran acknowledged any 3 items the screen was considered positive and the veteran was referred for further evaluation by a mental health professional qualified to diagnose PTSD. PTSD evaluation included a 17 item National Center for PTSD checklist for symptoms of military PTSD (PCL-M).{Department of Veterans Affairs, 2010 #3166} In addition, the mental health professional might also employ other PTSD evaluation instruments including the Mississippi Scale for Combat Related Posttraumatic Stress Disorder.{Keane, 1988 #3183} 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 (CAPS).{Blake, 1995 #3182} 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.{Peterson, 2011 #3184}”

17. Page 9, Line 56: Lists PTSD and PCL-M scores as separate dependent variables. Of what does variable “PTSD” consist? Is it the presence or absence of a diagnosis of PTSD? Clarification on this issue is recommended.

Response
The text was revised to indicate that the variable “PTSD” indicated the presence of PTSD.

18. Page 10, Lines 46-47: As presented here and throughout the manuscript, the authors refer to deployment length, but do not clarify the number of deployments. I was unclear as to whether the mean deployment lengths reported were for the deployment in which the injury occurred, or if it summed the length of all deployments of the veteran. Clarification is recommended.

Furthermore, it is recommended that mean number of deployments be reported here, as well.

Response
The number of deployments as well as the total length of deployment is provided. The end of the first paragraph of the Results section states:

“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)/40.7 ± 1.6 weeks (range 20 - 104 weeks) and combat veterans without LOC - 1.76 ± 0.25 deployments (range 1 - 4 deployments)/45.4 ± 6.5 weeks (range 20-104 weeks).”

19. Page 10, Line 56: Reference to PTSD – is this referring to number/severity of PTSD symptoms or
to frequency of PTSD diagnosis in the population? Clarification is recommended.

Response
The text was revised in accord with this comment, "Veterans with combat-acquired mTBI with LOC had low MOCA scores and high frequencies of a ND and the presence of PTSD (Table 1)."

20. Page 12, Line 10: Authors report 3.02 ± 0.20 episodes of LOC per veteran. A referral to Appendix 2 suggests that this is not a representative description of the case group. May be better to describe range and mean, rather than ascribing a "per veteran" rate.

Response
The Results were revised in response to this comment. The text was changed to, "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),"

21. Case control studies are understood to be a less vigorous form of empirical science than randomized control trials; however, given the nature of the research topic, the chosen study method is very appropriate. However, this limits the authors’ Discussion due to the fact that such a research approach can report correlation and not causation. Thus, it would have been helpful to a hear more about how the current study can be used to inform future research directions.

Response
In response to this comment the Discussion ends with the following paragraph:
"There is a tendency to attribute physical symptoms after deployment to PTSD rather than to mTBI.(Hoge, 2008 #2693) Future studies of combat TBI will determine the extent to which our findings of increased prevalence of PTSD and NDs with episodes of LOC generalize 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."

22. Would benefit from further discussion of the limitations of a possible self-selection bias. For example, veterans are often unaware of potential mTBI episode if not referred for further assessment. This does not preclude them having been injured by blast percussions without significant symptoms. Therefore, given that veterans are referred for further assessment in theater for a small number of the overall blasts to which they may be exposed, the veterans may be underreporting their injury history.

Response
In response to this comment, we expanded the discussion of the potential biases in this study.

23. Tables are somewhat difficult to read. Perhaps bolding to distinguish headings would be more reader-friendly.

Response
The tables were changed as suggested.

In summary, we appreciated the comments from the two reviewers and carefully revised the manuscript in response to the reviewer’s suggestions. The authors hope that the revised manuscript will be acceptable for publication. We will submit one version of the manuscript with all of the changes in highlighted text.

Sincerely,
# THE STUDY

1. Research question is not clearly defined - reads like an exploratory analysis. If so, needs to be stated.
2. Study design: since the research question is not clear, it follows that the study design was not tailored to the question.
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 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.
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.

# RESULTS & CONCLUSIONS

Please see above for issues regarding most of these. However, 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?

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

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.
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). 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? Interpretation of results fuzzy, and it is unusual to have so much research reviewed in the last sections of a research paper.

REPORTING & ETHICS

The article follows the Guidelines well - only problem area is developing reasonable conclusions from findings. 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.

GENERAL COMMENTS

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.

VERSION 2 – AUTHOR RESPONSE

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 number 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 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 tables 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.


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 correction.

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 (pBonferroni) adjusts the raw p-value (praw) for the number of times that a hypothesis is tested (number of comparisons = m), pBonferroni = m • praw. 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.
A case–control study examining whether neurological deficits and PTSD in combat veterans are related to episodes of mild TBI

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