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Loss of consciousness, but not etiology, predicts better working memory performance years after concussion

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1st editorial decision

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Ref.: Ms. No. JCTRes-D-19-00035
Loss of Consciousness, but not Etiology, Predicts Better Working Memory Performance Years after Concussion
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Dear Dr. Berryhill,

Reviewers have now commented on your paper. You will see that they are advising that you revise your manuscript. If you are prepared to undertake the work required, I would be pleased to reconsider my decision.

For your guidance, reviewers' comments are appended below.

If you decide to revise the work, please submit a list of changes or a rebuttal against each point which is being raised when you submit the revised manuscript.Also, please ensure that the track changes function is switched on when implementing the revisions. This enables the reviewers to rapidly verify all changes made.

Your revision is due by Mar 11, 2020.

To submit a revision, go to https://www.editorialmanager.com/jctres/ and log in as an Author. You will see a menu item call Submission Needing Revision. You will find your submission record there.

Yours sincerely

Nicholas G Murray, Ph.D.
Editorial Board Member
Journal of Clinical and Translational Research

Reviewers' comments:

Comments from the Editor:
Please clearly address the comments from both reviewers but the discussion does need substantial edits. Please make sure to include how your data is relevant to other data in the content area.

Reviewer #1: Please see the editorial comments:
1. Please address the numerous errors in your Reference citations. Start with the first citation.
2. Please take out abbreviations in the Abstract. Figure should not go in the abstract and depending upon where you chose to insert it please provide a "stand alonge" description.
3. pg 3, L40, "sentence" starting with Lasting cognitive..... does not make sense, rework.
4. pg 4, L53, "sentence" starting with Here, we seek.... does not make sense.
5. pg 5, L9, please provide rationale for use of EEG.
6. pg 5, L19, please consider taking out sentence is not clear and it does not belong here in the manuscript.
7. pg 5, L41, I am sorry, I read this a couple of times and I am still not clear why additional N was added and where they came from.
8. pg 6, L14, The mTBI group (should report the N to help the reader keep the groups clearly in mind).
9. Table 1. Is Time is specified in description but please consider indicating Years in Table. Is there a statistical significance between the group LOC?
10. pg 7, L7 Do you have any evidence that the monitor sizes do not play a role in the performance of the participants? If so please tell the reader.
11. pg 9, L7 "In both tasks....." remind the reader what two tasks.
12. Results section needs work, it was difficult to follow.
13. pg 12, L 23, Discussion. So it does appear you did not report the SS in WM between the groups, and if you did it was not clear to me. Even if this is a follow up study you should report the results from your initial work and then follow up with the predictive analysis.

Reviewer #2: The submitted manuscript titled "Loss of consciousness, but not etiology, predicts better working memory performance years after concussion" presents interesting factors to consider in concussion research. However, there are some major concerns in the methods, results and discussion that need to be addressed by the authors.
Abstract: The purpose statement of the study is not associated with the use of resting state EEG procedure. Please revisit the stated results in the abstract to specifically highlight the

effect of LOC on VWM (later and better need to be clarified).
* The purpose of a graphical abstract is to independently describe the findings to the reader. However, the graphical abstract provided in this paper did not serve this purpose and may have to be described better.
Overall, major concerns of this paper are in the methods and discussion sections. Please clearly state your hypothesis and consistently discuss them in your discussion. The authors fail to address the rationale for including resting state EEG in this paper. Further there is no explanation to insignificance in the EEG results in the discussion. Overall there is lack of reporting of new evidence found from this revised data set that should be consistent or an extension of the previous work (Arciniega, 2019) where the authors describe differences in VWM performance between Controls and mTBI participants. It was unclear as to why these results were not reported in the current paper. The authors also mentioned that they "included unreported data and combined the analyses across 4 separate VWM experiments", however the results for these were not reported or discussed. In general, there is a lot of ambiguity in description of the methodology and why certain analyses were performed. These need to be revisited and revised significantly.
Some minor revisions are as follows:
* In your resubmission, please remove all information that could identify you or the affiliated institute to ensure complete blinding.
* All terms should be accurately defined throughout the paper including the abstract. (Example: Working memory (WM), LOC should be defined when first introduced).
* Recheck all sections for grammar and consistency (page 5, 10: an mTBI, a mTBI)
* Figure 2: Highlight the n for each group as these are not consistent with the table. Were all controls excluded from the final analyses? Also include a legend consistent with the description to highlight LOC and no LOC.
* It was also unclear as to why a graphical abstract was included without any description of its representation after the abstract.
Other comments by section are provided below:
* Introduction:
o Is concussion only associated with future cognitive changes? A plethora of research studies suggest the immediate effects of concussion on cognitive abilities.
o Working memory (WM, page 3) is one of the functions under executive functions. Why is WM an important function of interest compared to other executive functions needs to be highlighted.
o Authors have highlighted findings within the purpose statement. Why are partial results reported in the introduction (page 5)?
* Methods:
o Authors indicate football and hockey are high impact sports. It would be beneficial to clarify the inclusion criteria for all high impact sports and the rationale behind it (based on literature or other).
o The authors did not provide the total number of participants in the mTBI group but did for the controls.
o There is a lack of explanation of the use of the two stimuli and the process by which participants were asked to perform these. Authors will need to revisit this section to provide detailed description of the research design and procedures unless this has been established in previous work. This should be done before introducing the stimuli with clear description of what was done.
* Results:
o Figure 2: please include a legend to describe LOC and no LOC.

* Discussion:
o Unless there was some error, the discussion is incomplete and insufficient.
o Authors used resting state EEG analyses in the study however did not have any justification for the nature of the results and address it in the discussion.

Author's reponse

Dear Dr. Murray,

Thank you and the reviewers for the thoughtful comments regarding our manuscript, "Loss of Consciousness, but not Etiology, Predicts *Better* Working Memory Performance Years after Concussion." We appreciate the opportunity to address concerns and we believe we fully addressed each issue raised by the reviewers. In particular, we made numerous textual changes for clarification, added significantly to the behavioral analyses in the results sections and discussion, and included a conclusions section.

Finally, a number of concerns were associated with formatting. We suspect this is because we followed the author instructions to submit, "your paper, your way without formatting rules until acceptance" and we believe we have correctly formatted the paper in this revision.

Thank you for the opportunity to improve and remediate deficits in the original submission. The revised manuscript is much improved based on the peer review process and we hope you will find it suitable for publication in *JCTRES.* In the sections below, we address each issue in turn. In the revised manuscript, the significantly altered text is shown in red ink.

Best regards,

Hector Arciniega

Signed for all authors

Reviewer #1:

1. Please address the numerous errors in your Reference citations. Start with the first citation.

- *We have now formatted the references per JCTRES format and reviewed our EndNote file to make sure the references are correct. We followed the 'your paper your way' option in*

which journal required formatting is delayed until acceptance. Our apologies for the frustration, it was not our intent to defy guidelines.

2. Please take out abbreviations in the Abstract. Figure should not go in the abstract

and depending upon where you chose to insert it please provide a "stand alone" description.

- *All abbreviations were removed from the abstract.*

- *The journal requests a stand-alone 'graphic abstract' that is unaccompanied by a caption. Thus, we kept the existence of the graphic abstract, but altered the figure to be much clearer to the reader the content that would be addressed in the paper.*

3. pg 3, L40, "sentence" starting with Lasting cognitive...” does not make sense, rework.

- *We rephrased this sentence (p.5) as follows:*
  “Despite the emerging evidence identifying the possibility of lasting cognitive changes long after mTBI, there is still a lack of research in understanding the long-term sequelae associated with a history of mTBI.”

4. pg 4, L53, "sentence" starting with Here, we seek.... does not make sense.

- *We rephrased this sentence (p.6) as follows:*
  “Our goal in these analyses was to identify predictors of later VWM deficits in undergraduates with a history of mTBI.”

5. pg 5, L9, please provide rationale for use of EEG.

- *Thank you for highlighting a section that needed clarification. By way of more complete answer, a challenge associated with mTBI diagnosis is that it does not have a reliable biomarker. We are using low-density EEG because resting state data might be sufficiently sensitive to detect neural abnormalities, even in a heterogeneous population. The low-density EEG is appealing because it is easy to use, well tolerated, and portable, and therefore, has potential for clinical diagnosis and/or monitoring of rehabilitation progress.*

- *This section is rephrased as follows (p. 7):*

“We also collected low-density rs-EEG data from three frontal electrodes sites to evaluate if changes in power spectral densities can predict later VWM performance. Previous findings using rs-EEG in mTBI participants report abnormalities following injury [53-58]. We were primarily interested in power spectral densities differences in mTBI, but also in evaluating if our portable low-density EEG system can detect neural changes commonly picked up by conventional EEG systems. Thus, the focus of this work is to better understand why some people are impaired years after mTBI and others are indistinguishable from those who have never had a mTBI.”

6. pg 5, L19, please consider taking out sentence is not clear and it does not belong here in the manuscript.

- *Removed as recommended.*

7. pg 5, L41, I am sorry, I read this a couple of times and I am still not clear why additional N was added and where they came from.

- *We apologize for the unnecessary confusion. We were trying to explain that the data came from participants who had completed a variety of different WM tasks, and to explain that some of the behavioral findings have been published from a subset of the participants (N=43; Exps. 3 and 4 from Arciniega et al., 2019). Since that publication, we continued to collect data and those new 50 participants are also included for a total of N = 93 participants with a history of mTBI.*

- *We rephrased the paragraph (p. 8) as follows: "Data from a total of 93 undergraduates with a history of mTBI were included. Data came from two sources. First, we re-analyzed data from a subset of the participants (N=43) who were described in a previous publication [39]. Second, we included more recently collected data who have not been previously reported (n=50) in a replication of the color change-detection task (Figure 1a). To evaluate the interaction across different experimental tasks collected from these samples we converted performance into z-scores computed from the appropriate control group data (n=93)."*

8. pg 6, L14, The mTBI group (should report the N to help the reader keep the groups clearly in mind).

- *The size of each group is now referenced (p. 8) as follows:*

The mTBI participants were divided into 4 groups as a function of mTBI etiology: non-sports (N=35), team sports (N=13), high-impact sport (N=27), individual sports (N=18); see Table 1. High-impact sports were classified using National Collegiate Athletic Association (NCAA) outcome measures using the annual national estimate rates during the 2009-10 to 2013-14 academic years.

9. Table 1. Time is specified in description but please consider indicating Years in Table. Is there a statistical significance between the group LOC?

- *The table is amended as requested.*
- There is a significant difference in WM performance between those reporting LOC and those without LOC (p14).

10. pg 7, L7 Do you have any evidence that the monitor sizes do <u>not</u> play a role in the performance of the participants? If so please tell the reader.

The reviewer raises an important detail. For each experiment, a single monitor was used were significant (control vs. history of mTBI). By collapsing across various experiments we note that several different monitors were used.

This is now clarified as follows (p9): "For different experiments a single monitor was used, and found significant group differences."

11. pg 9, L7 "In both tasks....." remind the reader what two tasks.

- We clarified the text and inserted a figure reference as follows (p. 12):
- *"In both of the WM change detection tasks (See Figure 1AB for diagrams of the color patch and line orientation versions of the task),"*

12. Results section needs work, it was difficult to follow.

- *We revised the results section to include behavioral data and to highlight the question addressed by each analysis and finding associated with each analysis. These revisions are shown in red font in the revised version (pp. 13-16).*

13. pg 12, L 23, Discussion. So, it appears you did not report the SS in WM between the groups, and if you did it was not clear to me. Even if this is a follow up study you should report the results from your initial work and then follow up with the predictive analysis.

- *We appreciate the reviewer's concern. The details of the original experiments are now described in the introduction (p. 6). We note that in that original paper, there were 4-experiments, and all 4 revealed an impairment of the history of mTBI group. Experiments 3 and 4 of that paper documented participants' etiology but were not sufficiently powered (at N=43) to provide insight regarding what predicted lasting consequences of mTBI. We rephrased this section to better motivate the more highly powered analyses included here.*

Reviewer #2:

Abstract: The purpose statement of the study is not associated with the use of resting state EEG procedure. Please revisit the stated results in the abstract to specifically highlight the effect of LOC on VWM (later and better need to be clarified).

- *We appreciate the note and added text to clarify the abstract.*

1. The purpose of a graphical abstract is to independently describe the findings to the reader. However, the graphical abstract provided in this paper did not serve this purpose and may have to be described better.

- *We agree with the reviewer and provide a different figure that attempts to more clearly convey the findings in a simple way. We acknowledge that we are not graphic designers and hope that the current figure more adroitly serves the reader.*

2. Overall, major concerns of this paper are in the methods and discussion sections.

Please clearly state your hypothesis and consistently discuss them in your discussion. The authors fail to address the rationale for including resting state EEG in this paper.

Further there is no explanation to insignificance in the EEG results in the discussion.

- *We appreciate the reviewer's concern regarding clarity and have heavily revised the paper with this in mind. In short, the aim was to revisit the question of 'what predicts later WM performance after mTBI' after having collected etiology data from a larger N. For the earlier work, at N=43, there was no hint of a relationship that could provide any insight accounting for the heterogeneity of WM performance in the history of mTBI group.*
- *Secondly, the rationale for including low density resting state EEG is now explicitly addressed (p.7).*

3. Overall there is lack of reporting of new evidence found from this revised data set that should be consistent or an extension of the previous work (Arciniega, 2019) where the authors describe differences in VWM performance between Controls and mTBI participants. It was unclear as to why these results were not reported in the current paper. The authors also mentioned that they "included unreported data and combined the analyses across 4 separate VWM experiments", however the results for these were not reported or discussed. In general, there is a lot of ambiguity in description of the methodology and why certain analyses were performed. These need to be revisited and revised significantly.
   - *We revised the article to be more clear and easier to follow on all of the fronts raised by the reviewer.*

   - *We note that these data provide insights aimed at more finely understanding why some undergraduates with a history of mTBI are impaired at WM tasks. The earlier publication simply reported a main effect – that at the group level, undergrads with a history of mTBI were impaired compared to their colleagues. There is tremendous heterogeneity in outcome and a main effect is a coarse measure. Having collected more data, we were able to test whether there was a relationship that could predict in whom WM performance would be poor. The observation that LOC predicted better outcomes is surprising to us because it is more typically associated with worse injury.*

Some minor revisions are as follows:

1. In your resubmission, please remove all information that could identify you or the affiliated institute to ensure complete blinding.

   - *We tried to accomplish this task, although the nature of the follow-up design makes it likely that someone could do a little detective work and identify the authors.*

2. All terms should be accurately defined throughout the paper including the abstract. (Example: Working memory (WM), LOC should be defined when first introduced).

- Apologies for this irregularity.

3. Recheck all sections for grammar and consistency (page 5, 10: an mTBI, a mTBI)

- Thank you for highlighting our unintentional irregularities.

4. Figure 2: Highlight the n for each group as these are not consistent with the table.

-We re-checked the table for consistency.

Were all controls excluded from the final analyses? Also include a legend consistent with the description to highlight LOC and no LOC.

-Control data were used to compute z-scores and this is described in section 2.4.

5. It was also unclear as to why a graphical abstract was included without any description of its representation after the abstract.

- We found it difficult to get detailed formatting instructions on the website. We see no mechanism for providing a caption and have remade the figure in the effort to be informational without being so confusing. Our apologies.

Other comments by section are provided below:
* Introduction:
1. Is concussion only associated with future cognitive changes? A plethora of research studies suggest the immediate effects of concussion on cognitive abilities.

- Concussion is nearly exclusively studied within the first few days to weeks post-injury. The standard course of medical treatment is a few weeks, and then, no follow up is typical if physical symptoms (headache, sleep problems, etc.) have resolved. Thus, a major contribution of work like ours is to re-evaluate if there are lasting cognitive changes associated with mTBI.

2. Working memory (WM, page 3) is one of the functions under executive functions. Why is WM an important function of interest compared to other executive functions needs to be highlighted.

- The importance of WM is now more clearly contextualized in the Introduction to make its importance with regard to upper level cognition (e.g., problem solving, fluid intelligence) more explicit (p. 7).

3. Authors highlighted findings within the purpose statement. Why are partial results reported in the introduction (page 5)?

We apologize for any confusion. The current paper evaluates predictors of an individual's poor visual WM performance rather than exploring the possibility of a group-level deficit, as we had done previously. We rephrased the language to better motivate and clarify the rationale and the pattern of results.

* Methods:

4. Authors indicate football and hockey are high impact sports. It would be beneficial to clarify the inclusion criteria for all high impact sports and the rationale behind it (based on literature or other).

- *The reviewer raises an excellent point. We had used the NCAA criteria, but discovered that we had accidentally excluded women's soccer from the high impact sports group. We reconducted all analyses with this corrected group membership (it did not change the overall pattern of results). This is now clarified (p.8).*

5. The authors did not provide the total number of participants in the mTBI group but did for the controls.

-This information is listed in Section 2.1 (Participants) and in Table 1.

6. There is a lack of explanation of the use of the two stimuli and the process by which participants were asked to perform these. Authors will need to revisit this section to provide detailed description of the research design and procedures unless this has been established in previous work. This should be done before introducing the stimuli with clear description of what was done.

- We truly apologize for overlooking this key aspect of the design. The details regarding the task assignment are referenced in methods sections 2.3.1 and 2.3.2, and in results section 3.1. In short, the challenge is that we have been underpowered in looking at some of these various factors (e.g., etiology). By collapsing across findings from several experiments we can begin to better understand what predicts long-term outcomes after mTBI. This is one small step towards understanding in whom deficits are apparent. With that information it may become more tractable to build rehabilitation interventions.

* Results:
7. Figure 2: please include a legend to describe LOC and no LOC.

- Completed.

* Discussion:
8. Unless there was some error, the discussion is incomplete and insufficient.

- *We added content to the discussion section to more broadly address the relevance of the findings (pp16-20).*

9. Authors used resting state EEG analyses in the study however did not have any justification for the nature of the results and address it in the discussion.

- *We added text in the introduction (p. 7) to provide rationale for this manipulation and we return to the EEG data in the expanded discussion (pp.16-17).*

2nd editorial decision

16-Mar-2020

Ref.: Ms. No. JCTRes-D-19-00035R1
Loss of Consciousness, but not Etiology, Predicts Better Working Memory Performance Years after Concussion
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Dear authors,

I am pleased to inform you that your manuscript has been accepted for publication in the Journal of Clinical and Translational Research.

You will receive the proofs of your article shortly, which we kindly ask you to thoroughly review for any errors.

Thank you for submitting your work to JCTR.

Kindest regards,

Nicholas G Murray, Ph.D.
Editorial Board Member
Journal of Clinical and Translational Research

Comments from the editors and reviewers:

Reviewer #1: Thank you for being responsive to reviewer comments. The manuscript reads much better. All the best.