Author’s response to reviews

Title: Monitoring Neurocognitive Functioning in Childhood Cancer Survivors: Evaluation of CogState Computerized Assessment and the Behavior Rating Inventory of Executive Function

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Author’s response to reviews:

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Dear Dr. Pertl,

Thank you for the opportunity to revise our manuscript, PSYO-D-18-00198 Monitoring Neurocognitive Functioning in Childhood Cancer Survivors: Evaluation of CogState Computerized Assessment and the Behavior Rating Inventory of Executive Function (Lyn Balsamo, Ph.D.; Hannah-Rose Mitchell, MPH; Wilhelmenia Ross, MPH; Catherine Metayer, MD, PhD; Kristina K. Hardy, PhD; Nina S. Kadan-Lottick, MD, MSPH).

The authors are particularly grateful for the insightful feedback regarding how to improve the quality of this paper. We have edited the manuscript in response to your and the reviewers’ comments as described in the point-by-point response below. Please also find the attached, revised copy of our manuscript with changes tracked. We hope that with these changes you will find the manuscript suitable for publication.

Sincerely,

Lyn Balsamo, PhD
Authors’ Responses

Editor Comments:

1. I echo Reviewer 2’s concern that the Conclusions drawn in the Abstract (and in some sections of the Discussion, see below) are not adequately supported by the data shown and should be tempered to reflect the poor sensitivity of the measures.

Response: Please refer to the response to Editor Comment # 7 and response to Reviewers’ Comments #1.

2. In the Abstract, only the sensitivity and specificity for mathematics is reported for the combination of both measures; for consistency, the figures for reading should also be reported.

Response: As suggested, we have now reported the sensitivity and specificity for reading are in the abstract.

3. It would be helpful to already flag in the Measures section that the cut-score for the CogState was determined by exploratory analysis and to direct the reader to the Analysis and Results sections for further information.

Furthermore, amending the information provided in the Analysis section to the following would provide greater clarity . . .

In addition, I would suggest rephrasing line 22 . . .

Response: Thank you for these suggestions which improve the clarity of the analysis. These changes were adopted and can be read on pages 6, 7, and 9.

4. Should line 224, Page 9 read “z < -1.5 (1.5 SD below the mean)”?

Response: Thank you for finding this typo. We made the correction.

5. From the Participant section on, use the term “participants” when referring to the patients who participated in this study to differentiate these individuals from the wider pool of patients who were approached for the larger study and childhood cancer patients in general.

Response: Thank you for this suggestion. We used the term “participants” in the paper for the context described.
6. Discussion, line 232, page 9: rephrase to “short questionnaires and/or computer assessments would identify…”

Response: Thank you. We edited the text as suggested.

7. Lines 243 and 248-249, page 10: Overstate the results as the sensitivity of these measures was poor (as acknowledged in lines 251 – 255).

Response: We edited the discussion to address this concern by emphasizing the poor sensitivity and low negative predictive value as well as removing some speculative sentences about implications for future testing. The text now reads, “Our data indicate that participants who show at-risk results on either monitoring measure are likely to demonstrate deficiencies in academic achievement. These measures can appropriate resources to individuals in need of comprehensive neurocognitive assessment. However, it is important to note that with poor sensitivity and low negative predictive value (NPV) the BRIEF-MCI and CogState Composite computerized assessment will not detect many pediatric cancer survivors that could benefit from comprehensive evaluation.”

8. The Discussion and Conclusion sections could give greater consideration to the research and clinical implications of this research and where to go from here. Reviewer 2 also gave some good direction in this regard;

Response: We also edited the Conclusion to now read, “With increasing numbers of pediatric cancer survivors, it will be important to have an easily and quickly administered monitoring tool, particularly in resource-limited communities, to identify those patients in need of comprehensive neurocognitive assessment. While individuals identified from the BRIEF-MCI or CogState Composite would likely benefit from a full neuropsychological evaluation given the strong specificity, use of these measures as screening tools is limited. They do not identify many patients with academic difficulties and in need of a full neuropsychological evaluation. Continued effort is required to find screening measures that have both strong sensitivity and specificity.”

Additionally, please refer to the response to Reviewer #2, Comment #3 and #4.
Reviewer #1

1. Generalizability to other populations needs to be discussed further, as does how these measures can be used in smaller institutions with less resources.

Response: Thank you for these important points. Regarding generalizability, we added a sentence to the Limitations section of the Conclusion (p. 12) which states, “Additionally, this study only examined cancer survivors who were at least 2 years from diagnosis rather than earlier in the therapy period so generalizations to these patients cannot be made.” We elected to use CogState as it was a promising tool being used in a multi-site Children’s Oncology Group (COG) clinical trial to assess cognitive function in this population. As harkened by the introduction, we reiterate more clearly in the conclusion (p. 11, paragraph 1) why computerized platforms may be beneficial in smaller institutions with less resources.

Reviewer #2

1. The authors might temper the conclusion in the abstract - as it stands, it appears as if both the BRIEF-MCI and CogState Composite have adequate sensitivity to detect those children in need of intervention; however, the results are quite the opposite. It might be more informative and transparent if this conclusion highlights the specificity of these tools and future implications of this work.

Response: We modified the conclusion of the abstract to reflect better the results. It now reads, “While individuals identified from the BRIEF-MCI or CogState Composite would likely benefit from a full neuropsychological evaluation given the strong specificity, use of these measures as screening tools is limited. With poor sensitivity, they do not identify many patients with academic difficulties and in need of a full neuropsychological evaluation. Continued effort is required to find screening measures that have both strong sensitivity and specificity.”

2. In the introduction (page 4, line 109), there is no clear explanation of the "computerized testing" being employed. It would be helpful to explicitly state how measures such as the CogState differ from the standard neuropsychological tests. I'm curious how such assessments reduce practice effects, especially since citation 14 doesn't provide any insight and even emphasizes that practice effects account for a large percentage of explained variance in cognitive changes over time.

Response: We provided better references (p. 4) that support the statement that these computerized assessments reduce practice effects. We also refer the reader to the Methods section where more detail about CogState is provided, such as who administers the tests (a research assistant) and the time required to complete (10-15 minutes).
3. It will also be important to consider how and if these tools adequately capture the full extent of cancer-related cognitive impairment. Page 11 highlights future leverage of newer computerized assessments of cognition; however, recent work has highlighted discordance between objective and subjective measures of cognition after cancer. What are the implications of this in pediatric cancer survivors specifically? Can we simply ask kids if they’re struggling academically? It would be helpful to flush this out a bit more.

Response: These tests assess domains of cognition typically affected by cancer treatment (1-3) and was adapted from the battery used in the multi-site COG study for children with high-risk ALL (COG AALL1131). These references were added to the manuscript (p. 6, paragraph 2). We also included verbiage in the discussion (page 11) to address your point, “A thorough history may include questions of patients, family, and/or teachers about grades earned, classroom behaviors, and performance.”

4. I wonder if there are other academic performance outcomes that can be used that may be more relevant to the cognitive tasks measured by CogState (attention, working memory, processing speed), such as daily classroom behaviors, grades, etc simply because the cognitive processes measured by CogState may not readily transfer to performance on the Connecticut Mastery Test or Academic Performance Test, thus attenuating any associations.

Response: We chose the Connecticut Mastery Tests because it was one of few standardized measures (maybe only) that was universally administered across the state and would provide an objective measure of academic performance. Because of the considerable variability among teachers, schools, and school systems, data generated by these sources would not appear to be standardized or reliable enough to use in a study of this nature. We agree with your point that there may be other downstream measures to capture better an association between neurocognitive processes and academics. We added a sentence to the Limitations section of the Conclusion (p. 12): “It may be promising to examine other downstream measures that are associated with neurocognitive issues, such as educational attainment; however, the length of follow up did not allow for that in this particular study(4).”

5. Understandably, the sample isn't large enough for stratified analyses, but are the authors able to provide more detailed treatment information in Table 1 (e.g., chemotherapy, radiation, neurosurgery)? This may have implications for the extent of cognitive dysfunction.

Response: We have included the requested information in Table 1.

