Reviewer's report

Title: Very long-term effects of cranial irradiation compared with intrathecal chemotherapy in treatment of childhood leukemia: A MEG study of brain oscillatory power differences correlated with cognitive dysfunction

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Reviewer: Jonathan Kleen

Reviewer's report:

This manuscript by Daams and colleagues examines long-term neurocognitive sequelae following childhood cranial irradiation treatment for leukemia. The authors present an interesting perspective by using MEG which provides excellent time and space localization of neurophysiological oscillation measures. They also provide data from patients that are decades out from their childhood treatments, giving a much stronger perspective on long-term quality of life than previous studies. The authors make a number of observations arguing that radiation treatment adds significant morbidity. Most of the conclusions relate to the findings in the theta and alpha bands, which the authors discuss in the context of previous literature on post-radiation cognitive impairment and accelerated brain aging.

This study adds important data to multiple fields of research and medicine. However there are some features that are somewhat unclear, and could be addressed to strengthen the manuscript. I have organized them by section.

Major recommendations

1. The authors describe the chemotherapy regimens for each group in the Methods section. Patients in the CRT+CT group had daunarubicin while those in the CT-only group did not. Since this is a potential interacting factor, it would be appropriate to address the potential interaction of daunarubicin neurotoxicity.

2. There is a statement in methods regarding a smaller head size for CRT group. This is intriguing and agrees with concepts in paper regarding worse cognitive outcomes. This needs a citation/reference, and are there any head size measurements for the different groups?

3. Regarding the excluded patients, it would be nice to know if the excluded patients had higher rates of psychiatric disease or CNS disorders in the CRT+CT vs. CT groups. This would add additional perspective as to post-radiation morbidity. If this is unknown please indicate so.

4. Statistical results (p values etc.) are only reported for the Global Relative Power section - please add the appropriate results to the text in the results so that the reader is not require to look them up in the extensive Supplementary tables.

5. Log-transformed variables are used, assumedly to help approximate gaussian
distributions given that most of the statistical tests used here assume this feature (e.g. Pearson's r). Were Shapiro-Wilk statistics performed on the log-transformed power values to verify normality? If not, could a different transform be used that would better-approach a normal distribution (e.g. square-root)? A sentence or two addressing this aspect in the Methods would particularly benefit those readers that are overly wary of power distributions in parametric statistics.

6. In the "Late effects of cranial irradiation" subsection, theta power is cited as a marker of pathology, and a citation of a general textbook is made. A large amount of emerging literature describes theta power as a reflection of active and successful cognitive processing depending upon the cortical region and the cognitive task at hand (see various recent literature by Dr. Michael Kahana for some examples and reviews). The argument of brain "slowing" made here may be technically valid given increased theta and decreased alpha are seen among those with irradiated brains. However, another interpretation could be that the increased theta power is reflective of compensatory processing by functional brain regions, such as that seen in unilateral prefrontal cortex following contralateral damage (see Voytek et al, 2010, in the journal Neuron). Essentially, a brief discussion of the differential interpretation of the findings is appropriate given the vast (especially recent) literature on cortical theta oscillations - similar to how alpha is discussed in the subsequent paragraph.

7. In the "Late effects of chemotherapy" subsection, CT is regarded as a superior alternative to CRT in terms of cognitive outcomes, but as a reader I am left wondering if survival rates and primary recurrence rates are also superior or if it is a trade-off between mortality and sequelae. Perhaps a sentence or two regarding these aspects would benefit the paper, particularly since the authors recommend to "completely abolish" CRT in the Conclusions subsection.

As a side note, a number of pathological and iatrogenic etiologies tend to affect the younger brain in terms of long-term cognitive outcomes. I am happy that the authors assessed whether there was an influence of either time since diagnosis, and more importantly age at diagnosis (an indirect index of age at treatment).

Minor recommendations
1. p3 line 15 - "suffers" should be “suffer”
2. p4 3rd sentence of Methods - there is an imbalance of parentheses
3. p5 line 8 confusing discrepancy as to whether 2 channels were excluded (151-149) or 7 channels as stated.
4. p10 line 5 - carriage return out of place
5. p10 line 19 - "careful selections have been made what to compare" should perhaps be "careful selections have been AS TO made what to compare"
6. Figure 2 - Could the authors perhaps show an additional graph with the log transformed values since the statistical results were performed on those and not the raw relative values? The non-transformed values shown are appropriately and unfortunately variable (large SDs), clouding the interpretation for the reader relative to the results discussed in the paper.
7. Figure 3 - Instead of "patient group" please indicate as CT+CRT group for clarity

Discretionary recommendations
1. The authors point out that the use of MEG and subjects decades out from their treatment are major strengths of this study. The benefits of MEG are discussed earlier in the paper but the benefits of the older subjects could be discussed more to enhance this importance of this factor (e.g. more robust estimates of long-term QOL, less interaction of possible active disease, etc.)

2. An initial paragraph (2-3 sentences) opening the Discussion section with a general recap might be appropriate to help readers tie the results together before delving into the subsections.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests: I declare that I have no competing interests.