Subject: Pediatric Research - Major Revision Decision on Manuscript ID PR-2024-1571
From: Pediatric Research <onbehalfof@manuscriptcentral.com>
Date: 2024-12-03, 7:06 a.m.
To: Alexander Weber <aweber@bcchr.ca>
CC: "tgcarmichael@outlook.com" <tgcarmichael@outlook.com>

03-Dec-2024

Dear Dr. Weber:

Manuscript ID PR-2024-1571 entitled "The Application of Magnetic Susceptibility Separation for Measuring Cerebral Oxygenation in Preterm Neonates", which you submitted to Pediatric Research, has been reviewed and the editors have given a major revision decision. The comments of the reviewer(s) and/or editor are included at the bottom of this letter. The reviewer(s) have recommended significant revisions to your manuscript. We invite you to respond to these comments and revise your manuscript.

To revise your manuscript, log into https://mc04.manuscriptcentral.com/prjournal and enter your Author Center, where you will find your manuscript title listed under "Manuscripts with Decisions." Under "Actions," click on "Create a Revision." Your manuscript number will be appended to denote a revision. Only the SUBMITTING author will be able to upload revised files. All coauthors are copied on this email for informational purposes only.

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You will be unable to make your revisions on the originally submitted version of the manuscript. Instead, please revise your manuscript using a word-processing program and save it on your computer before uploading your revised files. Your original files are available to you when you upload your revised manuscript. Please delete any redundant files before completing the submission.

Prior to uploading your manuscript files, you will need to save two versions of the manuscript text: (1) the tracked changes version showing your edits (termed 'Main Document, tracked-changes version' in the file-type menu), as well as (2) a "clean" version of the revised manuscript that does not show the tracked changes ('Main Document, clean version' in the menu). Both files should then be uploaded to the submission system.

When submitting your revised manuscript, you will be able to respond to the comments made by the reviewer(s) in the space provided. You can use this space to document any changes you make to the original manuscript. In order to expedite the processing of the revised manuscript, please be as specific as possible in your response to the reviewer(s).

In addition, it is critical for authors at the revision stage to upload publication-quality figure files. The Editorial Office will return your manuscript for correction if your figure files do not meet the following requirements:

*Figure resolution: must be at least 300 dpi (dots per inch) for color figures; 600 dpi for blots and black & white photographs; and 1000 dpi for graphs and illustrations.

*Figure format: files must be in .tif, .jpg, or .eps format

We have found the following web sites helpful for creating high-resolution figures: Gimp, "How to make a High Resolution image" and ISMTE's Publishing High-Quality Figures.

The Editor in Chief encourages submission of color figures for the online only version of the manuscript, which incurs no additional fees. Color figures are eligible for feature as the cover art and highlight in the Editor's Focus.

Springer Nature offers authors English Language Editing, Scientific Editing, Figure Services and more. Please visit their website for further information.

Because we are trying to facilitate timely publication of manuscripts submitted to Pediatric Research, your revised manuscript should be submitted by 01-Feb-2025. If it is not possible for you to submit your revision by this date, we may have to consider your paper as a new submission.

Once again, thank you for submitting your manuscript to Pediatric Research. We look forward to receiving your revision.

Sincerely,

Cynthia Bearer, MD, PhD
Editor-in-Chief, Pediatric Research

Eleanor Molloy, MB, PhD
Associate-Editor-in-Chief, Pediatric Research

Editorial Office email: info@pedres.org

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Editor Comments to Author:

Section Editor: 1
Comments to the Author:
This manuscript by Weber et al. is focused on oxygenation quantification in the SSS and CCV in 19 premature infants utilizing susceptibility mapping and paramagnetic separation, which is compared directly and thoroughly with the preceding literature using a variety of techniques. This is significant in that it may provide an additional, and hopefully more accurate, way to measure oxygenation in premature infants. Overall this is an impressive and well planned study.
- The main issue which needs to be addressed revolves around the conclusions, and that the presented data do not support that this has superior accuracy. It is important because some of the findings contradict previous studies. The language here needs to be softened
- In the methods, there are 3 lines where "***" appears, I am not sure what that is supposed to represent (lines 102, 104, 117).
- Requires additional clarification related to imaging analysis and how it leads to their conclusion

Reviewer(s)' Comments to Author:

Reviewer: 1

Comments to the Author
Summary:
This study aims to quantify oxygenation in the superior sagittal sinus and in central cerebral veins in a cohort of 19 preterm neonates using quantitative susceptibility mapping and the separation of its paramagnetic components.

The authors observed no significant differences between the oxygenation of the SSS and CCV, which contradicts previous results reported in the literature. They reported that the accuracy of the paramagnetic source separation was higher than QSM, but at the cost of an increased variability.

The methods of the manuscript are well detailed, and the results are appropriately compared to the literature. A few aspects require some clarification, see below.

One limitation of this work is the lack of sufficient data to support the claim of increased accuracy with susceptibility sources separation compared to QSM. In the absence of a ground truth and with results that contradict literature, this work does not support the increased accuracy claimed. The conclusion of the work should be re-written to better reflect the actual results.

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Specific Issues:

Abstract:
1.   Please re-write the first sentence of the conclusion section of the abstract to better reflect the results presented in this work, which do not fully support the current claim of increased accuracy with susceptibility source separation.

Introduction:
2.   It is mentioned that methods to assess whole brain oxygenation have been developed for adults and that they are starting to be explored in neonates. Please detail what are the challenges for transferring these methods to neonate population.

Method:
Image acquisition
3.   Please state in the text the plane of acquisition for each sequence.
4.   Table 1: The phase encoding row (2nd row) does not provide the phase encoding information. This row should be split in two, one for the acquisition plane information (axial, coronal, sagittal), and one for the actual phase encoding direction in plane (ex: right-left, antero-posterior, or head-foot).

Image analysis
5.   Briefly explain why the fifth echo was selected to generate the preliminary brain mask.
6.   Please clarify if all echoes were used for the preliminary QSM calculation.
7.   Can the authors expand on the motivation for choosing the STI software? What does 'cleanest images' refer to exactly (accuracy, artifact free, etc.)? Please also add a reference to support this statement.
8.   Can the authors explain why only the last three echoes were used for the STI QSM calculation?
9.   The methods description mentions that the last three echoes only were used for the STI calculation, but then in the parameters listed in the text, it is mentioned that a TE1=5 ms was used, which is the first TE of the sequence. Can the authors clarify this?
10.   In the paragraph describing the methods for the paramagnetic source separation, please list the TEs in ms unit instead of s for consistency with the rest of the manuscript. Also in the same paragraph, please use the acronym introduce earlier in the text for delta TE for consistency.
11.   Can the authors include an illustration of the final SSS and CCV masks used to calculate mean susceptibility in these regions?

Results
12.   Figure 2: Please add a label to the colorbars (ex: chi (ppm)). Also, please clarify in the caption what the x/y/z label on each figure refers to.
13.   Figure 3: In the text referring to fig 3, the graphs presented are referred to as boxplots, versus in the figure caption, they are referred to as violin plots. Please make sure to consistently use the same term.

Discussion
14.   The authors mention being the first to explore the susceptibility source separation technique in neonates, while it has been done in adult population. Please discuss the challenges of transferring this technique to a neonate population and how these were address in this work.
15.   Can the authors discuss why, based on their results, QSM underestimates the susceptibility compared to the paramagnetic component separation technique?