Peer Review File

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Reviewer A

This fascinating study (Functional neuroimaging of responses to multiple sensory stimulations in newborns with perinatal asphyxia) investigates the feasibility of performing functional near-infrared spectroscopy (fNIRS) as a surrogate to conventional functional magnetic resonance imaging (fMRI). The clinical population is newborns with perinatal asphyxia (PA) following hypoxic birth. The advantage of fNIRS is its mobility, less motion sensitive, and the ability to differentiate between oxy- and deoxyhemoglobin (HbO and HbR) whereas fMRI only detects deoxyhemoglobin as seen in the typical hemodynamic BOLD response. The downside of fNIRS compared to fMRI is even lower spatial resolution and limited anatomical information. While a stable hemodynamic response is observed in adults, variable responses are reported for the developing brain. This study also aims to establish a novel relationship between fMRI and fNIRS by directly comparing the two techniques using visual, auditory, and sensorimotor cues. While the study is very interesting, important and attempts to fill a knowledge gap in the field, there are a few minor issues that I think should be addressed.

Comment 1: The authors provide reasonable aims underlying the investigation but are missing a clearly stated hypothesis.
Reply 1: The authors added at the end of the Introduction section the hypothesis that there is a correlation between fNIRS and fMRI signals in each stimulus in newborns with PA.
Changes in the text: (see Page 7, lines 107-108)

Comment 2: Under the section Paradigm, it is stated that the infants had their eyes closed during visual stimulation. Is this correct, why would you want their eyes closed during a visual stimulus? Also, how did you keep track if their eyes were closed, was an eye-tracker used?
Reply 2: The authors assumed that the eyes were closed because the acquisitions during visual stimulation were accomplished under newborn sedation in fMRI and natural sleep in fNIRS. Nevertheless, we cannot be sure, so we removed that the infants had their eyes closed in the Paradigm section. We did not use an eye-tracker.
Changes in the text: (see Page 9, line 148)

Comment 3: A minimalistic description of the MRI protocol and fMRI analysis should be provided for transparency, and so that a reader does not have to track it down.
Reply 3: We appreciated the comment and added a summarized description of the MRI data acquisition and fMRI data preprocessing and analysis in the Methods section.
Changes in the text: (see Pages 9-11, lines 162-166 and 172-191)

Comment 4: The typical TE for adult fMRI is roughly 30 ms, and it has been shown that the HRF can take longer to peak in newborns (Cusack et al, Dev Cogn. Neurosci., 2018). Per reference (16), where the MRI protocol is detailed, why did you choose to use a TE of 31 ms in this newborn cohort rather than a longer TE? Was there an optimization/experimental design reasoning behind this choice?
Reply 4: We agree that the TE influences image contrast and signal-to-noise ratio and acknowledge the insightful comment of the reviewer. Despite a couple of empirical recommendations on the optimal TE for 3T fMRI newborn studies (ref 43), these were not available to our knowledge at the time of data acquisition. The previous studies had optimized TE for 1.5T which must be reduced by 25% when transposed to 3T MRI scanner. Therefore, a longer TE was not used. However, by using a shorter, suboptimal TE, we incurred a risk of not detecting significant signal changes instead of claiming spurious effects that would support undue conclusions. Furthermore, to improve the detection of signal changes and strength of neural response, we optimized the stimulation protocol and the HRF model in the data analysis (ref 15 and 20). We expand the discussion on this issue according to the reviewer's comment.
Changes in the text: We added this issue in the Limitations section (see Page 17-18, line 334-338)

Comment 5: In the fMRI fNIRS comparison, did you look to see if the PA fMRI BOLD did not correlate with the control fNIRS?
Reply 5: We focused on establishing a relationship between the fMRI and fNIRS signal in the group of participants with PA to understand whether fNIRS can be a surrogate marker for fMRI on the newborn's bedside. Therefore, no correlation was performed between the fMRI signal of newborns with PA and fNIRS controls. Throughout the manuscript, we clarified the intragroup correlation performed.
Changes in the text: (see Page 3, line 57; Page 5; Page 14, line 263; Page 16, line 303; Page 29, line 539; Page 31, line 575)

Reviewer B

This is a pilot study comparing fMRI to fNIRS in 20 patients with perinatal asphyxia to 6 control patients.
Only one of the control patient had MRI. Based on the several limitations listed by the authors it is unclear if any meaningful information can be gathered from such small patient numbers.
Reply to Reviewer B: We recognize the relatively small sample size with 18 newborns with perinatal asphyxia (PA) and six controls. Nevertheless, the main aims of this exploratory study were to probe the feasibility and to establish a relationship between two distinct functional neuroimaging modalities signals. Considering the efforts required to obtain the functional data from both techniques, the small sample can provide preliminary data for a larger future study that answers specific questions, concerning the correlation between fNIRS and fMRI signals.

It would have been helpful to compare fMRI data from PA newborns with controls. However, parents' consent was understandably difficult to obtain in those cases, owing to the sedation implied by the procedure.

Moreover, despite the transparency of limitations in the Discussion section, this study has several strengths: improvement of the knowledge concerning the characterization of functional brain responses in newborns, specifically in PA. The multiple sensory stimulations performed during the same acquisition session permit support that the variability of the responses found also reported in the literature may be explained by physiological/biological mechanisms, not artifacts. Observing the fNIRS-fMRI relationship may enhance the clinical use of fNIRS at the bedside as an alternative functional imaging tool to fMRI in newborns with PA.