Assessing Regional Cerebral Oxygen Consumption ($CMRO_2$) in Preterm Neonates: A Quantitative MRI Cohort Study with Exploratory Analysis of Respiratory Support

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ABBREVIATIONS: ASL = arterial spin labeling; $CMRO_2$ = cerebral metabolic rate of oxygen; $CSaO_2$ = cerebral arterial oxygen saturation; $CSvO_2$ = cerebral venous oxygen saturation; GA = gestational age; CGM = cortical grey matter; DGM = deep grey matter; Hct = hematocrit; NICU = neonatal intensive care unit; NIRS = near-infrared spectroscopy; OEF

= oxygen extraction fraction; PMA = post-menstrual age; PPM = parts per million; QSM = quantitative susceptibility mapping; T2-TRIR = T2 Prepared Tissue Relaxation Inversion Recovery; TRUST = T2-relaxation-under-spin-tagging;

Summary Section

PREVIOUS LITERATURE: Quantitative estimates of brain oxygen consumption can be achieved using oxygen-15 PET or xenon clearance techniques, which measure cerebral blood flow but are invasive and involve ionizing radiation, limiting their use in neonates. A less invasive option is near-infrared spectroscopy (NIRS), which estimates cerebral venous oxygen saturation ($CSvO_2$) but is limited to regional assessments and superficial brain tissue. Non-invasive MRI techniques have been explored, including venous oxygenation measurements with TRUST MRI, MR susceptometry, and T2-TRIR MRI pulse sequences, showing feasibility in neonates and correlating well with previous methods.

KEY FINDINGS: Using a novel, non-invasive MRI technique and analysis pipeline, CBF and $CMRO_2$ values were measured in very preterm neonates at TEA and found to align closely with reference values. CBF and $CMRO_2$ values were associated with time in room air and non-invasive ventilation.

KNOWLEDGE ADVANCEMENT: We introduced a novel MRI technique and analysis pipeline, and demonstrated that non-invasive respiratory support in very preterm infants is associated with increased cerebral oxygenation and consumption, while room air is linked to lower values. Regional brain analysis revealed that respiratory support impacts different brain structures uniquely.

Abstract

BACKGROUND AND PURPOSE: Developing a non-invasive method for measuring oxygen consumption at both regional and whole-brain levels in preterm infants is crucial for assessing brain development and neuronal injury in this vulnerable population. This study presents a multi-modal MRI technique and analysis pipeline designed for this purpose, which we employ in a cohort study to investigate how the duration of various respiratory supports in very preterm infants affects CBF and the cerebral metabolic rate of oxygen ($CMRO_2$).

METHODS: Infants (n=19) born <32 weeks gestational age were recruited in the neonatal intensive care unit. Infants were scanned at term-equivalent age using a 3T MRI sequence comprising of T_1-weighted, T_2-weighted, arterial spin labeling (ASL), and SWI. Days on three different categories of respiratory support, based on levels of invasiveness, were recorded. Using multiple linear regression, CBF and $CMRO_2$ were analyzed against days on: respiratory support, days in room air, and the proportion of days on respiratory support; GA and PMA were used as confounding factors.

RESULTS: Average CBF and $CMRO_2$ of cortical grey matter was 14.3 ± 4.25 mL/100g/min and 29.49 ± 29.49 µmol/100g/min, respectively. $CMRO_2$ and CBF were positively correlated with days on non-invasive respiratory support, and negatively correlated with days in room air.

CONCLUSION: Using our novel method, CBF and $CMRO_2$ values aligned closely with literature values. Our exploratory findings suggest that the type of respiratory support may influence cerebral oxygenation during the neonatal period in infants born very preterm, with greater oxygen delivery and consumption associated with non-invasive respiratory support. Our regional brain analysis further highlights that different brain structures are impacted in distinct ways.

Introduction

The developing brains of preterm infants are vulnerable to injury and dysmaturation, which can result in long-term neurological deficits (Kiechl-Kohlendorfer et al. 2009). Infants born very preterm (32 weeks gestation) are particularly at risk for significant short and long-term respiratory problems, and the lower the gestational age at birth, the more likely the infant may be negatively impacted (Chung, Chou, and Brown 2020). To mitigate these risks, it is crucial to monitor brain hemodynamics, as instability in oxygen delivery and metabolism can contribute to these injuries (Dhillon et al. 2022). These infants are also at significant risk of respiratory disorders, such as respiratory distress syndrome (McPherson and Wambach 2018), and bronchopulmonary dysplasia (Yoder, Albertine, and Null 2016). Finding ways to prevent these respiratory disorders, and support lung development, is critically important as lung health helps determine the amount of oxygen the brain receives (Cannavò et al. 2020;

Guillot et al. 2020). Therefore, close monitoring of cerebral oxygenation is critical to identify these risks early and apply neuroprotective strategies that may mitigate long-term neurological consequences.

In the NICU, to aid in respiration and improve lung function, various strategies including different forms of ventilation can be used, where the general goal is to decrease days of invasive mechanical ventilation. Non-invasive modes of ventilation, such as continuous positive airway pressure and nasal intermittent positive pressure ventilation, have been shown to be effective in lowering rates of complications and mortality compared to intubation with mechanical ventilation (Kalikkot Thekkeveedu et al. 2022; Ho, Subramaniam, and Davis 2020; Ackermann et al. 2023; Shi et al. 2014). With advances in neonatal intensive care and the use of less invasive forms of respiratory support, the incidence of bronchopulmonary dysplasia and other respiratory complications in preterm neonates has decreased over time (Dumpa and Bhandari 2021). However, the optimal mode and timing of ventilation in preterm neonates with respiratory disorders are still being debated (Brown and DiBlasi 2011; Greenough and Sharma 2005; Ramaswamy et al. 2020; Kollisch-Singule et al. 2022)

Non-invasive MRI-based techniques are actively being explored to assess whole-brain oxygen consumption. One approach combines non-invasive venous oxygenation measurements from the sagittal sinus using T2-relaxation-under-spin-tagging magnetic resonance imaging (TRUST (Lu and Ge 2008)) with flow measurements from phase-contrast MR angiography, which has been used in adults (Xu, Ge, and Lu 2009) and has shown feasibility in neonates (Liu et al. 2014; Qi et al. 2018). Another method combines MR susceptometry to measure venous oxygenation in the sagittal sinus with phase-contrast MR angiography (Jain et al. 2011). Studies using this technique in neonates demonstrated that the results correlate well with those obtained through diffuse optical and correlation spectroscopy methods (Jain et al. 2014). Still another method applied in neonates is the T2 prepared tissue relaxation inversion recovery (T2-TRIR) MRI pulse sequence (Petersen, Lim, and Golay 2006), which measures the transverse and longitudinal relaxation rate of blood (T_{2b} and T_{1b}) in the sagittal sinus, and venous oxygenation subsequently derived from the T_{2b} and the T_{1b}-derived hematocrit (Lu et al. 2012).

In the current study, we propose a new method using quantitative susceptibility mapping (QSM) and arterial spin labeling (ASL) – in combination with hematocrit (Hct) and pulse oximetry – to determine regional whole-brain cerebral metabolic rate of oxygen ($CMRO_2$) and CBF. In order to investigate the validity of this new non-invasive approach we compared the obtained results to previously reported reference values (Altman et al. 1993; De Vis et al. 2014; Liu et al. 2014; Elwell et al. 2005; Skov et al. 1993; Yoxall and Weindling 1998; Qi et al. 2018). In addition, we conducted an exploratory analysis to evaluate if the technique can detect whether the degree of lung disease, as indicated by the duration of time on different levels of respiratory support in very-preterm neonates, is correlated with brain oxygenation measures $CMRO_2$ and CBF in different brain regions at term-equivalent age. We hypothesized the $CMRO_2$ and CBF would be negatively correlated with time on invasive respiratory support.

Methods

STROBE

The methodology and its reporting have followed the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) standards. We include the checklist for a cohort study in our Supplementary Materials.

Patients

The study was approved by the Clinical Research Ethics Board at the *** and written informed consent was obtained from the parent/guardian for each infant.

Preterm neonates born <32 weeks gestational age (GA) (n=20) admitted to the level III neonatal intensive care unit (NICU) at *** in *** were recruited by a research nurse from February 2021 to January 2022. Our sample size was determined based on similar recruitment numbers from previous studies (Altman et al. 1993; De Vis et al. 2014; Liu et al. 2014; Elwell et al. 2005; Skov et al. 1993; Yoxall and Weindling 1998; Qi et al. 2018). Inclusion criteria were infants born less than 32 weeks GA. Infants were excluded if there was evidence of a congenital malformation or syndrome, a TORCH infection, or ultrasound evidence of large periventricular hemorrhagic infarction (>2 cm, Grade 4 intra-ventricular hemorrhage). Parents were approached by the research nurse about the study shortly before being discharged from the NICU. Infants returned to the hospital for the study at TEA (37-44 weeks PMA) for the MRI scan. One infant remained in hospital on respiratory support at 44 weeks PMA, and was withdrawn from the study. The final number of infants scanned was 19. The clinical characteristics of the subjects are shown in Table 1.

MRI data acquisition

All scans took place at the *** 's MRI Research Facility and were performed on a 3.0 Tesla General Electric Discovery MR750 (scanner software version DV26.0_R03) with a SREE Medical Systems single channel neonatal head coil. Infants were fed and swaddled by a research nurse prior to being placed in an MRI compatible incubator for imaging (SREE Medical Systems). Molded foam was placed around the infant's body and head to minimize head movement and ear plugs were used for ear protection. Arterial oxygen saturation and heart rate were monitored and measured continuously throughout the scan using a pulse oximeter placed on the foot of the infant. A neonatologist *** and primary investigator *** were present throughout the scan.

MRI scans were performed using a protocol consisting of a T1-weighted scan, a T2-weighted scan, a pseudo-continuous ASL scan to measure CBF, an SWI scan to generate QSM maps, and a diffusion weighted imaging spin echo EPI sequence (not included in this report). Sequences were repeated when large motion artifacts were detected. If an infant awoke or was moving during the scan, the scanning was stopped, and a research nurse entered the MRI room to monitor and ensure the infant fell back to sleep.

The T1-weighted coronal 3D-FSPGR parameters were: 2.97ms TE, 7.74ms TR, 12 degrees flip angle, 20cm FOV, 512x512 matrix, 0.39x0.39 mm in-plane resolution, 1mm slice thickness, 126 slices, and a scan duration of 4min39 s. The T2-weighted sagittal 3D-CUBE parameters were: 66.29ms TE, 2,300ms TR, 90 degrees flip angle, 20cm FOV, 256x256 matrix, 0.78x0.78 mm in-plane resolution, 1mm slice thickness, 106 slices, and a scan duration of 5min1s.

The pseudo-continuous ASL axial multi-shot spiral 3D fast spin-echo parameters were: 10.55ms TE, 4.68s TR, 111 degrees flip angle, 24cm FOV, 128x128 matrix, 1.875x1.875 mm in-plane resolution, 4mm slice thickness, 50 slices, 1,450ms label period, 2,025ms pulse label delay, 24 control-label pairs, and a scan duration of 5min26 s.

The SWI axial 3D spoiled GRE flow compensated parameters were: five equally spaced echoes, 5ms first TE, 5.24ms echo spacing, 30.9ms TR, 20 degrees flip angle, 25cm FOV, 256x256 matrix, 0.977mm in-plane resolution, 2mm slice thickness, 92 slices, and a scan duration of 5min29s.

A DWI spin-echo EPI sequence was also acquired, but was not analyzed for this study.

Clinical data collection

Hct values were acquired retrospectively from chart review. Hct values for the day of scan were predicted using a four-parameter Weibull function (`drc`; `fct=W1.4`; Supplementary Figure 1). Clinical variables were obtained from the ***. Days on respiratory support were categorized into three groups: Category 1 (invasive ventilation) included high frequency jet ventilation, high frequency oscillatory ventilation, and intermittent positive-pressure ventilation (either volume or pressure targeted); Category 2 (non-invasive ventilation) included non-invasive positive pressure ventilation and continuous positive airway pressure; and Category 3 included high-flow and low-flow nasal cannula. The three categories represented the invasiveness of respiratory support, with Category 1 being the highest, and Category 3 being the lowest.

MRI data processing

Imaging data was processed using an in-house pipeline written in `Bash` shell script by *** with minor edits by ***. A step-by-step summary of the pipeline can be found in the Supplementary Materials.

Statistics

Statistical analysis was performed using `R` (v. 4.4.3) (R Core Team 2022) and `R studio` (v. 2022.12.0 Build 353) (RStudio Team, n.d.). A multiple linear regression analysis was conducted to examine relationships between dependent variables CBF or $CMRO_2$ and independent variables (e.g. days on Category 1 support). GA at birth and post-menstrual age (PMA) at time of scan were included as confounding factors. The correlation coefficient, p-value, and beta value was determined for each individual analysis. Significant relationships were considered with a p-value of 0.05. Multiple comparison corrections were not applied as our analysis was primarily exploratory.

Using a multiple linear regression analysis including GA and PMA as confounding factors, CBF and $CMRO_2$ were analyzed separately against days on: the three separate categories of respiratory support, the number of days in room air (total days in the NICU minus total days on respiratory support), and the proportion of days on respiratory support (total days on respiratory support divided by total days in the NICU). Previous studies have shown a significant negative relationship between the brainstem volume of very preterm neonates at TEA and prolonged days on mechanical ventilation (Guillot et al. 2020); thus the days on Category 1 respiratory support was analyzed with brainstem volumes.

Results

Median (Q1-Q3) GA at birth and PMA at scan were 28.86 (27.79–29.93) and 40.57 (39.29–41.36), respectively. Median (Q1-Q3) days on Categories 1, 2, and 3 respiratory support, in room air, and length of stay in the NICU were 2 (0–4), 19 (11.5–32), 7 (5.5–12), 11 (3.5–23), and 53 (37–60), respectively (Table 1 and Figure 1).

A subject-by-subject distribution of days on different categories of respiratory support is shown in Figure 2.

Gestational age at birth was found to be negatively correlated with both days on Category 1 (invasive ventilation) and Category 2 (non-invasive ventilation) respiratory support, but not Category 3 (high-flow/low-flow; Figure 3).

A sample of results of the MRI analysis, including a sample brain segmentation, CBF map, QSM map, and $CMRO_2$ map are shown in Figure 4.

Mean whole-brain $CSvO_2$, $CSaO_2$, Hct and oxygen extraction fraction (OEF) values were 63.9 $\pm$ 4, 98.3 $\pm$ 1.5, 29.7 $\pm$ 3.5, and 34.9 $\pm$ 4.3, respectively. Regional mean CBF and $CMRO_2$ values are shown in Table 2. The lowest CBF and $CMRO_2$ values were found in the WM, while the highest CBF and $CMRO_2$ values were found in the brainstem.

Multiple linear regression analysis of regional $CMRO_2$ and CBF showed significant positive correlations with proportion of days on respiratory support (Figure 5), days on Category 2

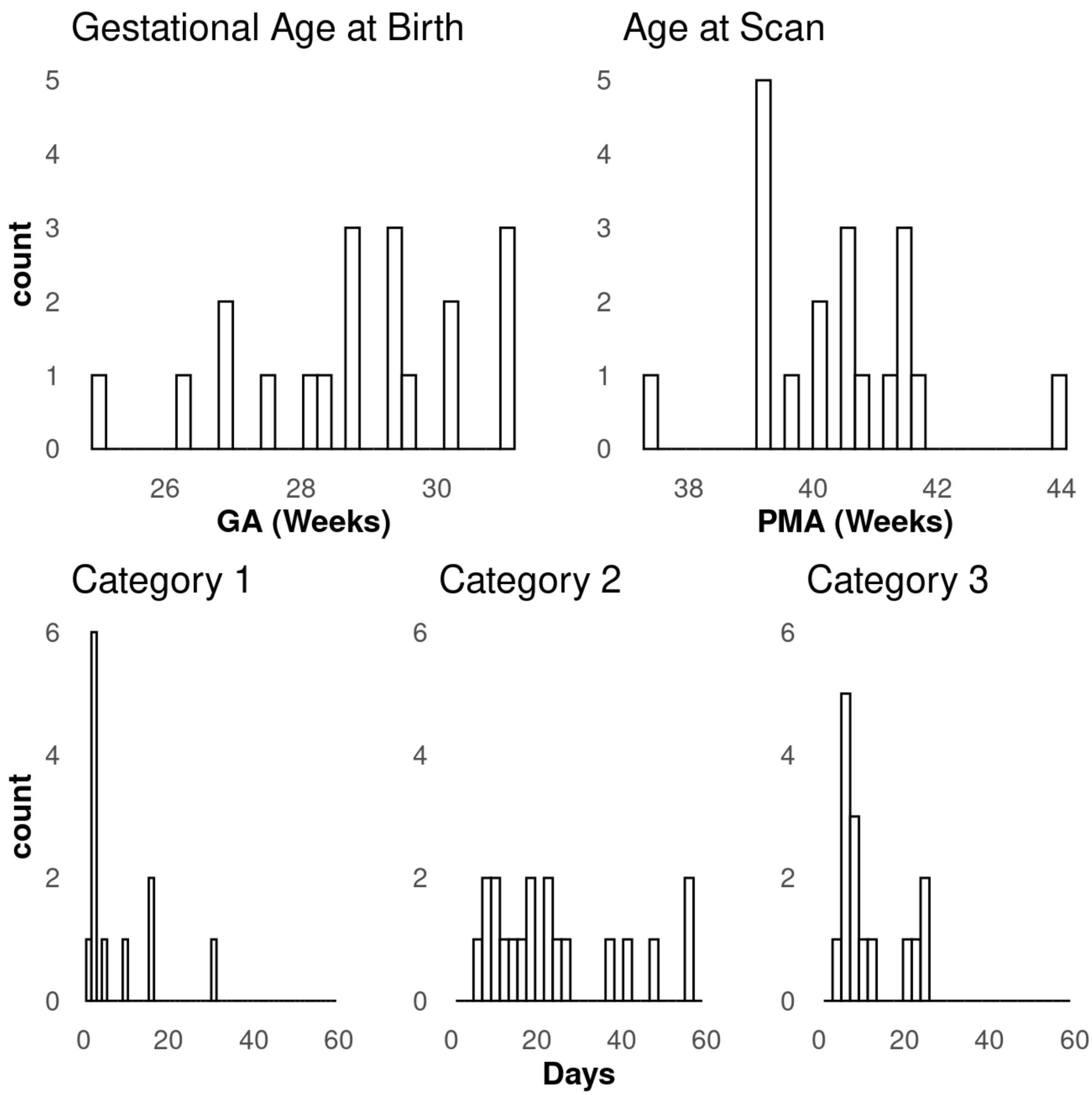

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Figure 1. **Types of respiratory support in relation to gestational age at birth, postmenstrual age (PMA) at scan, and days on each type of respiratory support.** Note, counts of 0 days on respiratory support are not shown. Category 1 = invasive ventilation; category 2 = noninvasive ventilation; category 3 = high-flow and low-flow support.

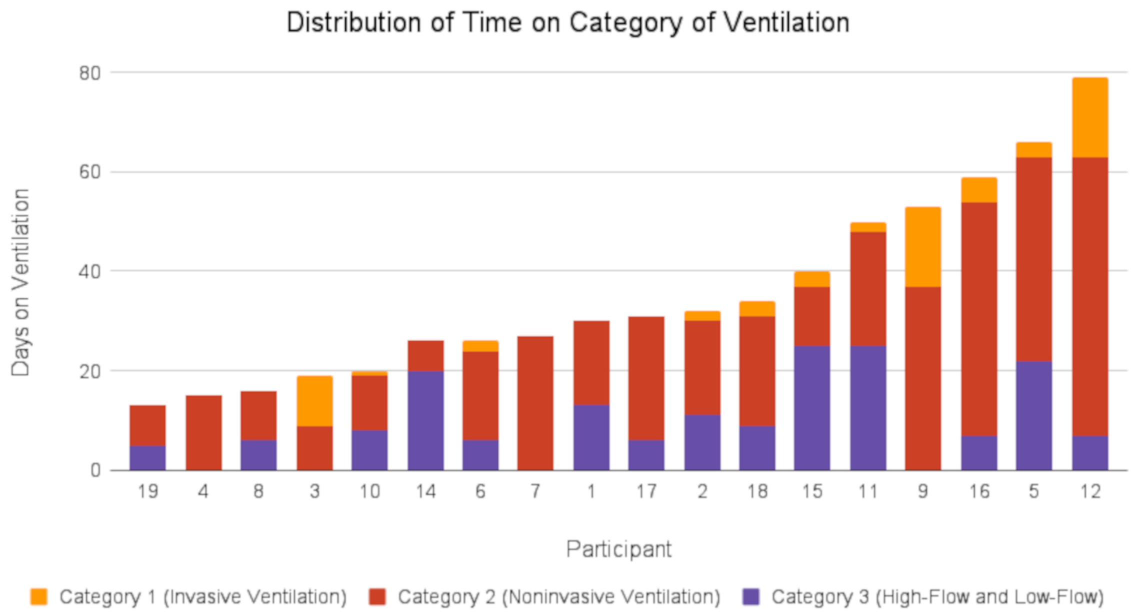

Figure 2. Days on the three levels of respiratory support for each study subject.

respiratory support (Figure 6), and significant negative correlations with days in room air (Figure 7). Results are summarized in Table 3.

No significant relationships were found between respiratory support categories and OEF, $CSvO_2$, $CSaO_2$, Hct (Table 3). No significant relationship was observed between brainstem volume and days on Category 1 respiratory support.

Discussion

We presented the initial results of a novel, non-invasive MRI method and analysis pipeline to evaluate $CSvO_2$, OEF and $CMRO_2$ in preterm neonates. The values we found agreed well with earlier reported reference values. In addition, our technique allowed us to examined the effects of various forms of respiratory support on CBF and $CMRO_2$ in neonates born very preterm. We found that the proportion of days on respiratory support was positively associated with both CBF and $CMRO_2$ in all brain regions, a negative association was found for both CBF (some brain regions) and $CMRO_2$ (all brain regions) with days in room air, and non-invasive ventilation showed a positive association with CBF in all regions, and a positive association with $CMRO_2$ in the brainstem and cerebellum.

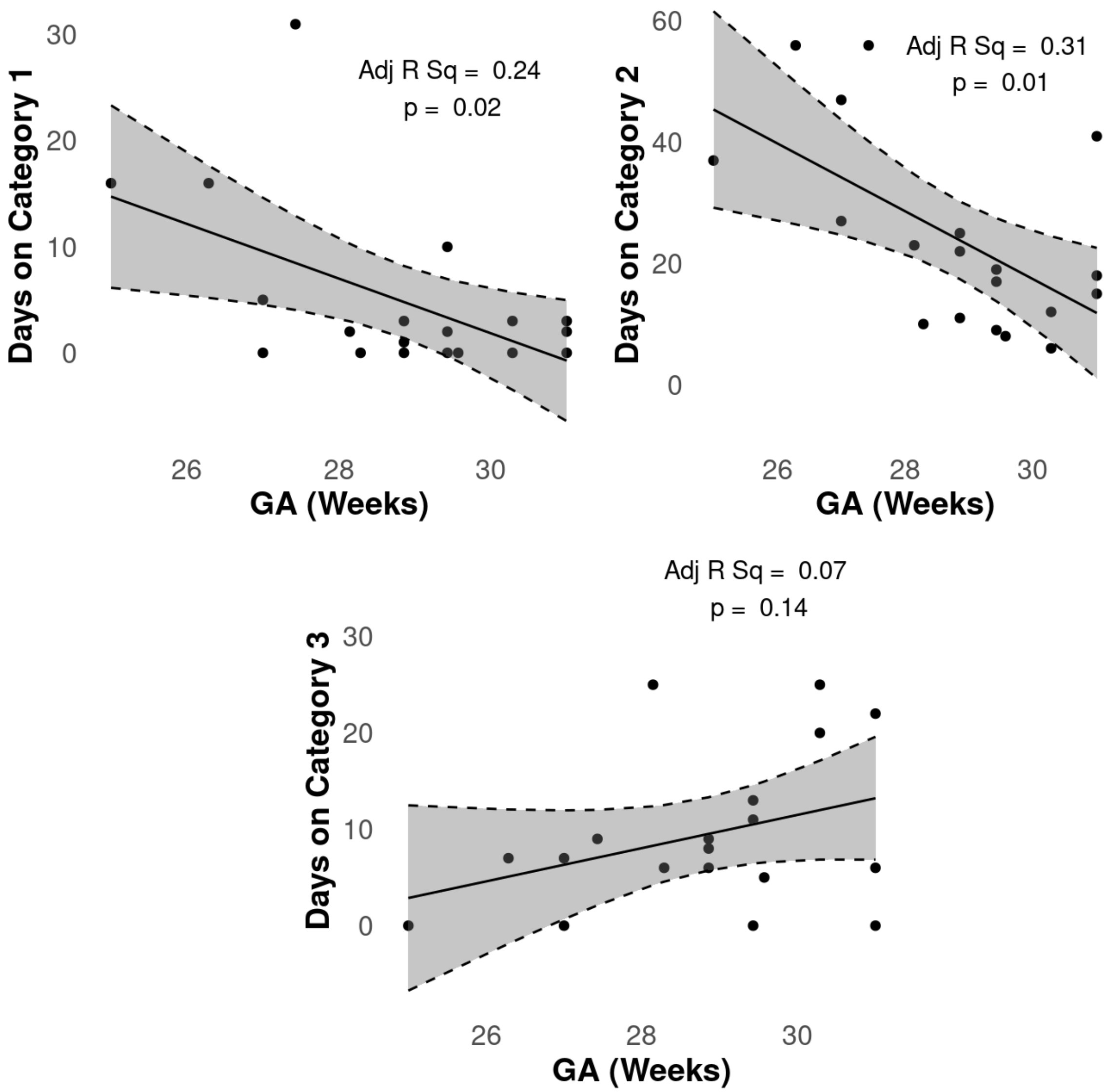

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Figure 3. Linear regression of days on the three categories of respiratory support vs gestational age.

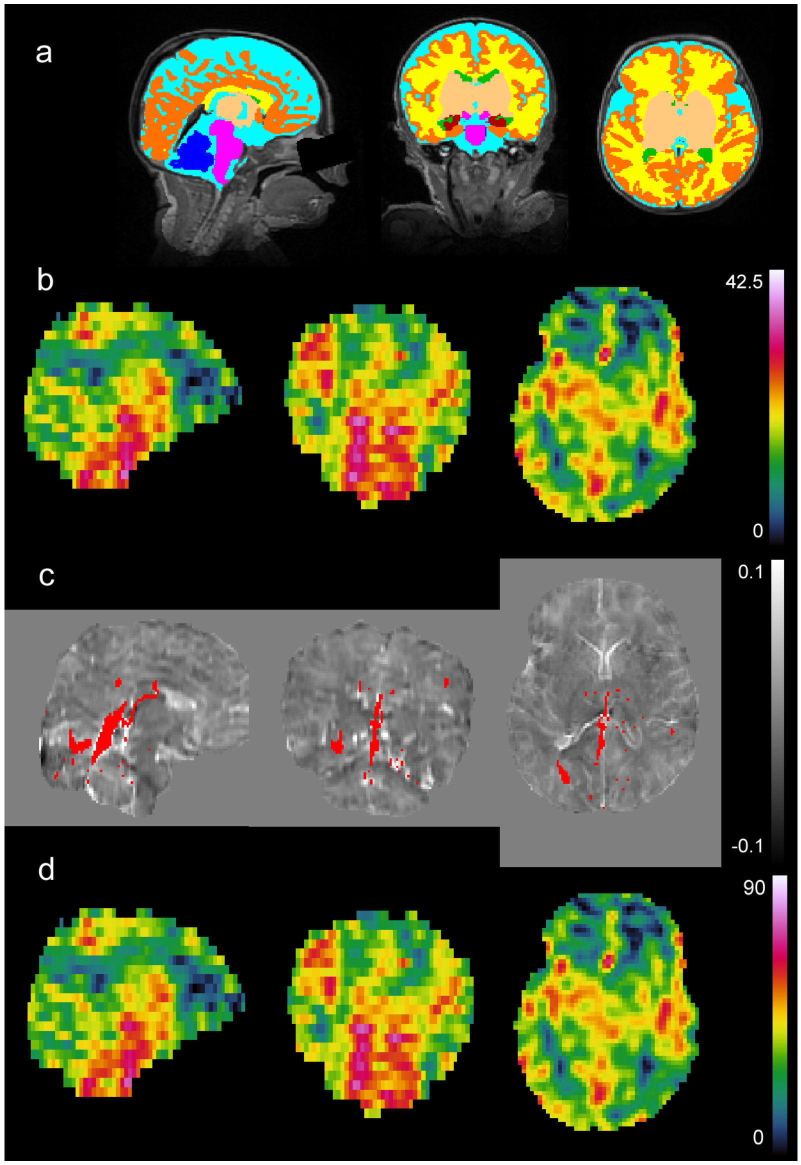

Figure 4. **Sample images from a subject of various MRI results.** All images show a sagittal, coronal and axial slice from left to right. A) is a T2w image in the background with segmentation overlaid in various colors: dark blue = cerebellum; pink = brainstem; light blue = CSF; yellow = white matter; dark orange = cortical grey matter; green = ventricles; light orange = deep grey matter; dark red = hippocampus and amygdala. B) is a processed CBF map from 0 to 47.5 mL/100g/min. C) is a QSM image in the background from -0.1 to 0.1 ppm susceptibility overlaid with a venous mask in red. D) is a processed $CMRO_2$ image from 0 to 93 µmol/100g/min. Note that B) and D) look identical as D is simply B multiplied by a value determined by $CSaO_2$, $CSvO_2$, and Hct. However, this value will be different for every subject.

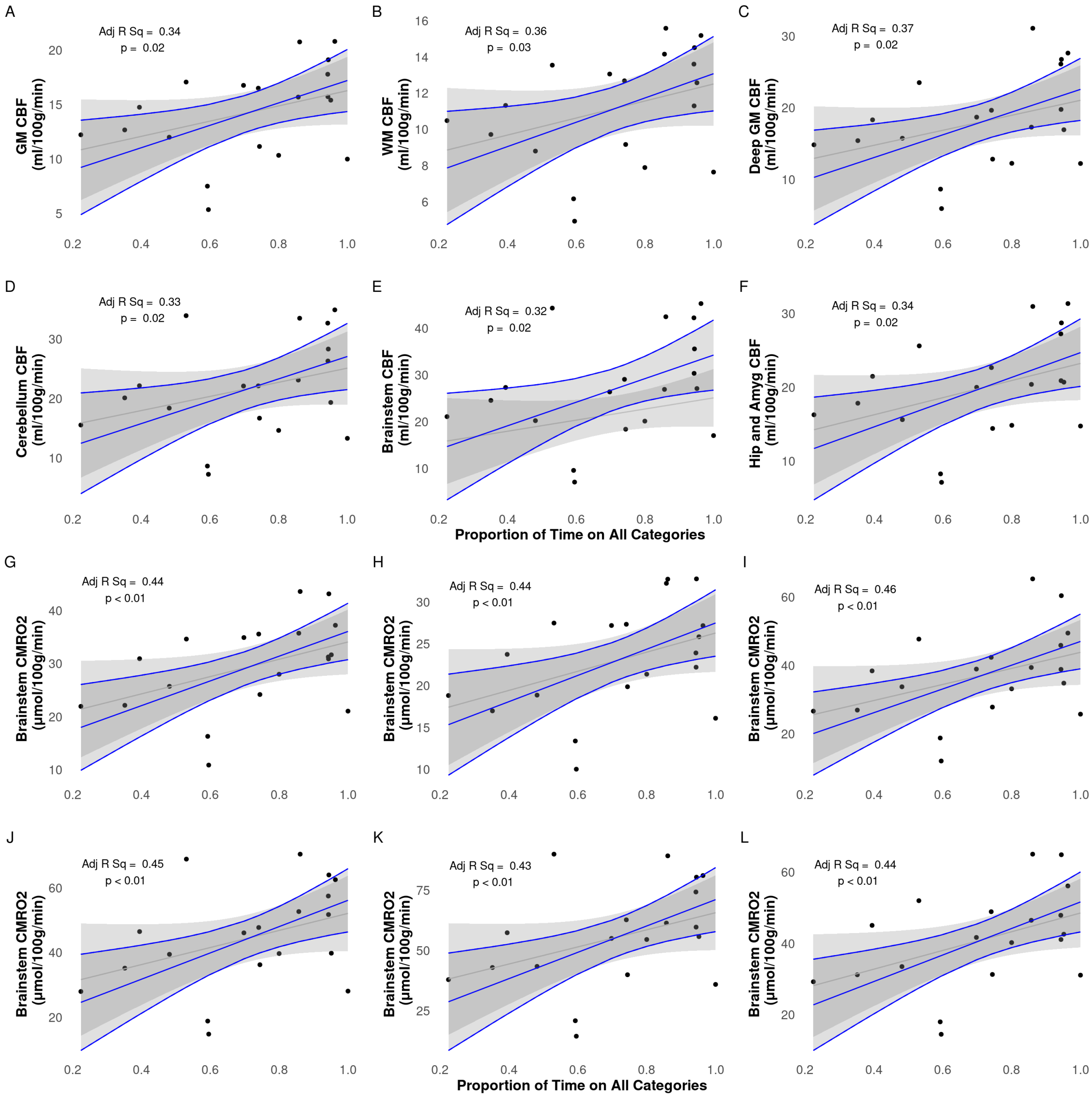

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Figure 5. CBF (A-F) and CMRO$_2$ (G-L) vs proportion of time on all categories while in the NICU. Raw data points as filled black circles. Grey line and ribbon represent linear model of raw data points and 95% interval, respectively. Blue line and ribbon represent adjusted multiple linear regression including GA and PMA as confounding factors.

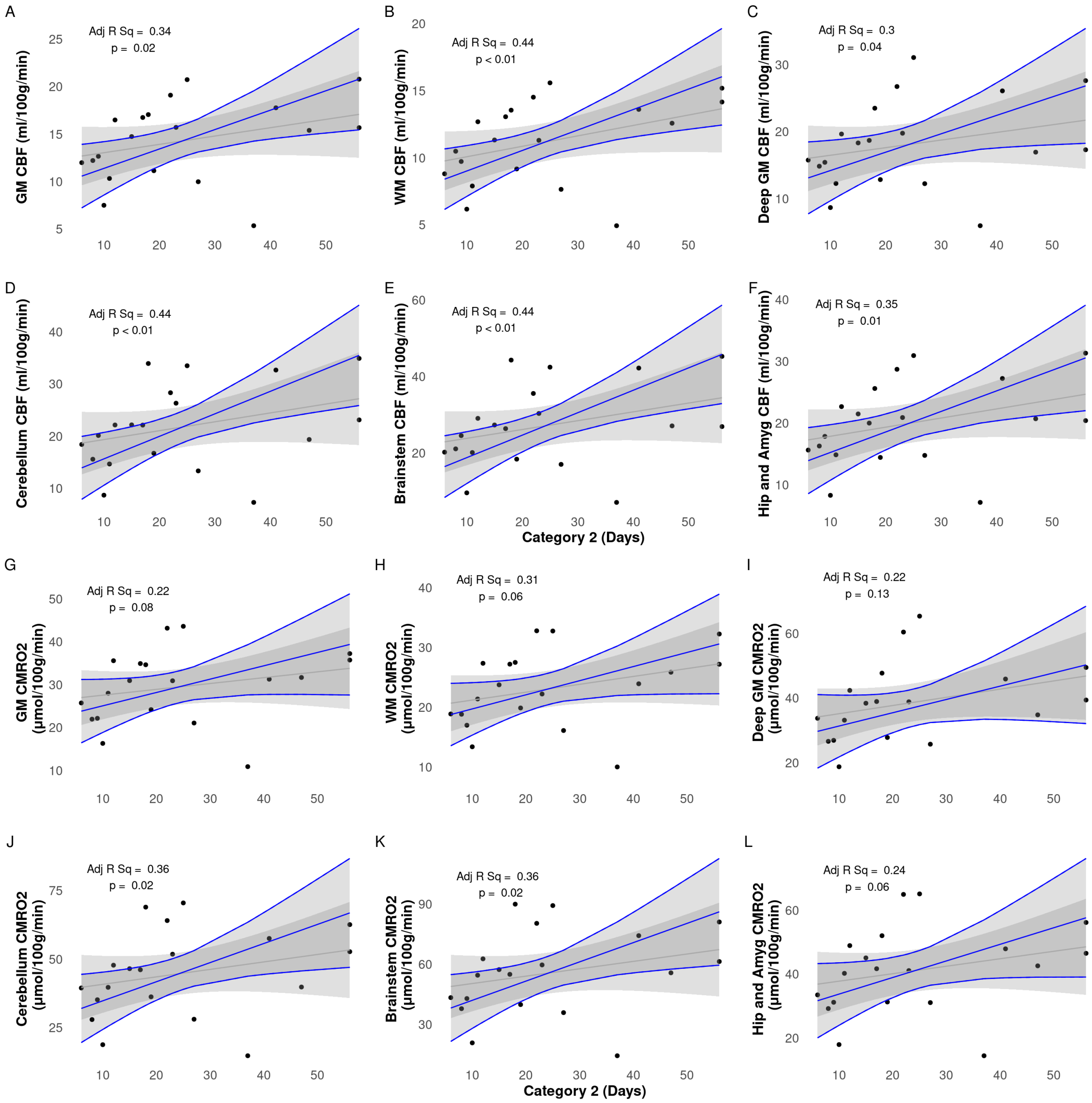

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Figure 6. CBF (A-F) and CMRO$_2$ (G-L) values against Days on Noninvasive Ventilation (Category 2). Raw data points as filled black circles. Grey line and ribbon represent linear model of raw data points and 95% interval, respectively. Blue line and ribbon represent adjusted multiple linear regression including GA and PMA as confounding factors.

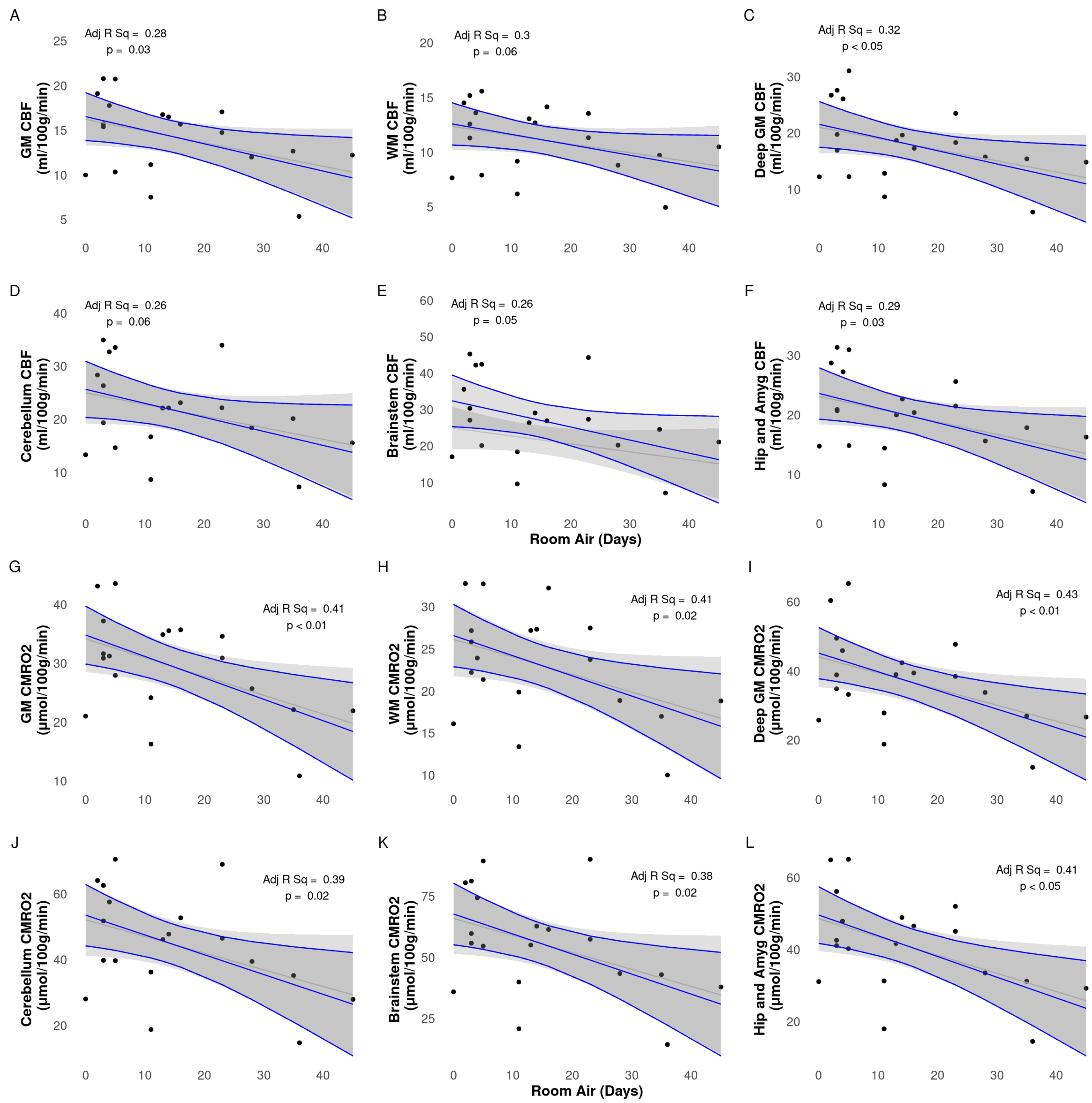

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Figure 7. CBF () and CMRO$_2$ (b) values vs days in room air. Raw data points as filled black circles. Grey line and ribbon represent linear model of raw data points and 95% interval, respectively. Blue line and ribbon represent adjusted multiple linear regression including GA and PMA as confounding factors.

Comparison of MRI methods with previous literature

The results from previous neonatal studies are summarized in Table 4. The global $CMRO_2$, CBF, OEF and $CSvO_2$ values from this study align well with the literature from MRI, NIRS and PET studies reported for TEA infants.

One strength of using ASL compared to similar studies that used phase-contrast to calculate CBF is the ability to look at regional changes in CBF as opposed to a single number for the whole-brain (Liu et al. 2014; Qi et al. 2018). This is best demonstrated in the difference we see when looking at correlations with Category 2, where all regions were found to have a positive correlation with CBF, but only the brainstem and cerebellum were found to be positively correlated with $CMRO_2$. This discrepancy is discussed more below. However, using ASL in infants also has drawbacks that should be considered, including low signal-to-noise ratio, quantification difficulties due to uncertainty in labelling efficiency and bolus arrival time, and the rapid changes that occur in such young populations that make single-imaging-protocol difficult (Liu et al. 2019).

Similarly, a strength of using QSM to study $CSvO_2$ rather than previous MRI methods that used the TRUST (Liu et al. 2014; Qi et al. 2018) or T2-TRIR (De Vis et al. 2014), is that QSM produces a whole-brain map with high spatial resolution. By producing a whole-brain map, we were able to measure the $CSvO_2$ by averaging over all internal veins. This is likely to produce a more robust measurement than acquiring a single slice and averaging within the superior sagittal sinus (SSS) as TRUST and T2-TRIR do. For the current study, our QSM maps were reconstructed to a 0.9x0.9x0.9mm^3 resolution, but future studies would benefit from acquiring and reconstructing up to 0.5x0.5x0.5 mm$_3$. Indeed, greater spatial resolution would likely improve $CSvO_2$ measurements as χ values could be better isolated to venous tissue without including non-venous sources. Finally, QSM could also allow for regional analysis of $CSvO_2$ values, which we did not attempt here. Unfortunately, as our method for calculating QSM requires removing brain tissue along the edge of the brain (an eroded brain mask), we could not measure $CSvO_2$ values in the SSS for more direct comparisons. Future work should be directed at acquiring QSM values in the SSS.

Two of the studies that measured $CMRO_2$, CBF and $CSvO_2$ in sick newborns requiring ventilatory support did not investigate associations between these values and days on various forms of respiratory support. Therefore, we were not able to directly compare these findings.

Respiratory support

In the present study, more days in room air without any type of respiratory support was associated with lower $CMRO_2$ and CBF values. If the assumption of higher $CMRO_2$ and CBF are indications of more optimal brain health, then this may suggest that the use of some form of respiratory support may be more beneficial to very preterm infants than weaning to room air. Indeed, $CMRO_2$ and CBF were positively related to the proportion of time on respiratory support compared to the total time in the NICU. However, caution must be advised when interpreting these findings. Our study was observational, therefore, we cannot exclude various confounding factors, such as various levels of illness which would have dictated the form of respiratory support the infant received. We may be observing a compensatory effect, wherein infants who were sicker may have over-compensated for CBF and $CMRO_2$ to provide adequate oxygen. This would imply that increased $CMRO_2$ and CBF are a reflection of higher illness severity. It is critical for future studies to further explore this relationship because, if on the other hand, being in room air indicates suboptimal cerebral oxygenation and metabolism, it may significantly influence how infants in the NICU are managed.

Furthermore, while all brain regions were found to have a negative correlation between days in room air and $CMRO_2$, this was not the case for CBF, where only the cortical grey matter, deep grey matter, and hippocampus & amygdala were found to be negatively correlated with days in room air. Specific brain structures appear to regulate the level of CBF differently and independently of $CMRO_2$, suggesting that these brain regions may be more susceptible to or protected from hypoxia. Indeed, evidence for physiological uncoupling of CBF and $CMRO_2$ has been reported previously (Fox and Raichle 1986; Henriksen et al. 2021; Ishii et al. 1996). However, caution should be exercised when drawing strong conclusions from our exploratory analysis.

Invasive ventilation was not found to have to be associated with $CMRO_2$ or CBF in any tissue regions. This was unexpected as we hypothesized that infants who required more days on invasive ventilatory support would have lower $CMRO_2$ values at TEA. We also did not find a relationship between invasive mechanical ventilation and brain stem volume at TEA, unlike a previous study by Guillot et al. (2020) (Guillot et al. 2020). Our results are likely limited by the low exposure of this population to invasive mechanical ventilation, as only one infant required invasive support for a prolonged period of time ($>$ 28days).

Non-invasive ventilation support was associated with increased $CMRO_2$ and CBF in preterm neonates at TEA. The observed increase in $CMRO_2$ and CBF with non-invasive ventilation *suggests* that prioritizing non-invasive over invasive ventilation may improve brain health outcomes in preterm neonates. However, caution should be exercised as our findings are exploratory in nature. Future studies on respiratory support strategies should incorporate $CMRO_2$ and CBF measurements to better understand their relationship with cerebral oxygenation and include a healthy term control cohort to establish comparative baseline values.

The difference between elevated $CMRO_2$ and CBF was also observed within regional tissues where CBF increased in all regional tissues for infants on non-invasive ventilation, but $CMRO_2$ only increased in the brainstem and cerebellar tissue. One possibility for this observation could be that compensatory mechanisms are activated in response to respiratory distress or regional brain injuries that hinder the uptake of oxygen. As with our findings in room air, this suggests that specific brain regions respond to respiratory support differently and may be more susceptible to damage. However, further research is first required to reproduce our exploratory findings.

Limitations

There are several limitations that are worth highlighting. Our $CSvO_2$ processing pipeline filtered out χ values below 0.15 ppm in order to obtain realistic values. Future studies may wish to use smaller voxel sizes, as well as a technique to decompose paramagnetic and diamagnetic values in order to avoid this step (Shin et al. 2021). See a recent study of ours for an attempt at this technique (Carmichael et al. 2025). Furthermore, in order to reduce QSM artifacts, the exterior of the brain mask was eroded, making it impossible to measure $CSvO_2$ in the SSS. Future studies may find a way to measure QSM in the SSS, which would also allow researchers to determine if $CSvO_2$ values are different in the SSS compared to the central cerebral veins. Again, see a recent study of ours that attempted this (Carmichael et al. 2025). Hct levels were not collected on the day of the scan, but instead were predicted based on past values. Our respiratory support analysis was exploratory with a small sample size. Thus, the positive correlation we found in Category 2 may be spurious or a result of an unaccounted factor. Future studies using large sample randomized controlled trials would provide a clearer understanding of the relationship between respiratory support and cerebral oxygenation. Imaging was performed at term-equivalent age after the infants had been discharged from the NICU, meaning the scans were performed weeks after the infants were last on respiratory support. Obtaining scans while the infants are still receiving respiratory support could provide a more robust mechanistic connection. Our study did not include a healthy control cohort to compare the expected physiological measures at TEA. This would be important to include, as too much oxygen can be just as harmful as not enough (Rantakari et al. 2021). Finally, due to our sample size, this study did not explore supplementary variables, such as medications, that may affect respiratory uptake and oxygen metabolism, and patterns of oxygen saturations infants experience during their NICU stay.

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Tables

Table 1. Neonatal and maternal characteristic of the study sample.

Maternal Characteristics (n=19)		Neonatal Characteristics (
Gestational Diabetes	6 (31.6%)	Male (n)
Delivery Mode		Female (n)
Cesarean	16 (84.2%)	Birth weight (g)
Vaginal	3 (15.8%)	GA at Birth (weeks)
Maternal Fever		PMA on Scan Day (weeks)
Yes	1 (5.3%)	Weight on Scan Day (g)
No	6 (31.6%)	Head Circumference on Scan Day (cm)
Unknown	12 (63.2%)	Days in NICU
Chorioamnionitis		Days on Sedatives
Yes	4 (21%)	Days on Narcotic Infusion
No	12 (63.2%)	Days on Category 1 (invasive ventilation)
Unknown	3 (15.8%)	Days on Category 2 (non-invasive ventilation)
Leukocytosis		Days on Category 3 (high-flow/low-flow)
Yes	1 (5.3%)	Total Days on Respiratory Support
No	4 (21%)	Days in Room Air
Unknown	14 (73.7%)	
Gestational Hypertension	3 (15.8%)	
Pre-Existing Hypertension	1 (5.3%)	
Systemic Antibiotics		
Yes	15 (78.9%)	
No	1 (5.3%)	
Unknown	3 (15.8%)	

Median(Q1-Q3) is shown for continuous variables and n (%) for categorical variables. GA = gest
postmenstrual age on the day of the scan.

Source: Article Notebook

Table 2. Regional mean ± standard deviation CBF and CMRO2 values. White matter tissue was found to have the lowest CBF/CMRO2 values, while the brainstem had the highest. CBF = cerebral blood flow; CMRO2 = cerebral metabolic rate of oxygen; ROI = region of interest; CGM = cerebral grey matter; WM = white matter; DGM = deep grey matter.

ROI	CBF (mL/100g/min)	CMRO2 (μmol/100g/min)
CGM	14.3 ± 4.25	29.49 ± 8.62
WM	11.18 ± 3.11	23.08 ± 6.47
DGM	18.1 ± 6.63	37.22 ± 13.23
Brainstem	27.16 ± 11.05	55.69 ± 21.34
Cerebellum	21.78 ± 8.27	44.68 ± 15.98
Hippocampus and Amygdala	19.98 ± 6.85	41.14 ± 13.69

Table 3. Results from linear regression of physiological parameters with days on various forms of respiratory support. All analyses included GA and PMA as confounding variables. CGM = cortical grey matter; WM = white matter; DGM = deep grey matter; BS = brainstem; Cereb = cerebellum; H&A = hippocampus and amygdala.

ROI	Invasive Ventilation (Category 1) [95% CI] / Adj R^2	Noninvasive Ventilation (Category 2) [95% CI] / Adj R^2	High-flow and low-flow air (Category 3) [95% CI] / Adj R^2	Proportion Of Days On All Categories [95% CI] / Adj R^2	Room Air [95% CI] / Adj R^2
CBF					
CGM	0.05 [-0.31 to 0.41] / 0.02	**0.2 [0.05 to 0.36] / 0.34**	0.13 [-0.14 to 0.4] / 0.08	**10.27 [2.17 to 18.37] / 0.34**	**-0.15 [-0.29 to -0.02] / 0.28**
WM	0.08 [-0.17 to 0.32] / 0.13	**0.15 [0.05 to 0.26] / 0.44**	0.07 [-0.12 to 0.26] / 0.14	**6.7 [0.86 to 12.55] / 0.36**	-0.1 [-0.19 to 0] / 0.3
DGM	-0.05 [-0.59 to 0.5] / 0.06	**0.28 [0.02 to 0.53] / 0.3**	0.16 [-0.26 to 0.57] / 0.1	**15.82 [3.51 to 28.13] / 0.37**	**-0.23 [-0.44 to -0.03] / 0.32**
Cereb	0.18 [-0.5 to 0.87] / 0.07	**0.43 [0.14 to 0.72] / 0.44**	0.21 [-0.31 to 0.73] / 0.09	**18.81 [2.98 to 34.64] / 0.33**	-0.26 [-0.53 to 0.01] / 0.26
BS	0.17 [-0.75 to 1.09] / 0.05	**0.59 [0.2 to 0.97] / 0.44**	0.21 [-0.49 to 0.92] / 0.06	**25.22 [3.9 to 46.53] / 0.32**	-0.36 [-0.72 to 0] / 0.26
H&A	0.05 [-0.53 to 0.63] / 0.02	**0.33 [0.08 to 0.59] / 0.35**	0.13 [-0.31 to 0.57] / 0.04	**16.73 [3.73 to 29.73] / 0.34**	**-0.25 [-0.47 to -0.03] / 0.29**
$CMRO_2$					
CGM	0.04 [-0.68 to 0.77] / 0.04	0.31 [-0.04 to 0.66] / 0.22	0.25 [-0.29 to 0.79] / 0.1	**23.31 [8.19 to 38.44] / 0.44**	**-0.36 [-0.62 to -0.11] / 0.41**
WM	0.13 [-0.39 to 0.64] / 0.14	0.24 [-0.01 to 0.48] / 0.31	0.15 [-0.24 to 0.54] / 0.16	**15.68 [4.38 to 26.98] / 0.44**	**-0.36 [-0.62 to -0.11] / 0.41**
DGM	-0.19 [-1.27 to 0.89] / 0.09	0.41 [-0.13 to 0.95] / 0.22	0.3 [-0.52 to 1.12] / 0.12	**34.74 [11.97 to 57.5] / 0.46**	**-0.54 [-0.92 to -0.16] / 0.43**

ROI	Invasive Ventilation (Category 1) [95% CI] / Adj R^2	Noninvasive Ventilation (Category 2) [95% CI] / Adj R^2	High-flow and low-flow air (Category 3) [95% CI] / Adj R^2	Proportion Of Days On All Categories [95% CI] / Adj R^2	Room Air [95% CI] / Adj R^2
Cereb	0.27 [-1.03 to 1.56] / 0.1	**0.7 [0.11 to 1.29] / 0.36**	0.39 [-0.59 to 1.38] / 0.13	**40.71 [12.88 to 68.54] / 0.45**	**-0.6 [-1.08 to -0.12] / 0.39**
BS	0.2 [-1.55 to 1.96] / 0.07	**0.96 [0.17 to 1.75] / 0.36**	0.4 [-0.95 to 1.74] / 0.09	**54.63 [16.85 to 92.4] / 0.43**	**-0.82 [-1.46 to -0.18] / 0.38**
H&A	0 [-1.15 to 1.15] / 0.04	0.52 [-0.03 to 1.07] / 0.24	0.25 [-0.63 to 1.13] / 0.06	**37.23 [13.28 to 61.17] / 0.44**	**-0.58 [-0.98 to -0.17] / 0.41**
$CSvO_2$ (%)					
Wholebrain	-0.16 [-0.51 to 0.2] / -0.1	0.06 [-0.14 to 0.25] / -0.13	-0.06 [-0.34 to 0.22] / -0.15	-0.68 [-10.72 to 9.36] / -0.16	-0.02 [-0.19 to 0.14] / -0.15
$CSaO_2$ (%)					
n/a	-0.05 [-0.18 to 0.08] / 0.06	-0.06 [-0.12 to 0] / 0.23	0.02 [-0.08 to 0.12] / 0.03	0.34 [-3.23 to 3.91] / 0.02	-0.01 [-0.07 to 0.05] / 0.02
OEF (%)					
Wholebrain	0.13 [-0.26 to 0.52] / -0.14	-0.1 [-0.31 to 0.11] / -0.1	0.07 [-0.23 to 0.38] / -0.15	0.83 [-10.03 to 11.68] / -0.17	0.02 [-0.16 to 0.19] / -0.17
Hct (%)					
n/a	-0.19 [-0.49 to 0.12] / -0.07	-0.02 [-0.2 to 0.15] / -0.18	-0.05 [-0.3 to 0.19] / -0.17	2.35 [-6.48 to 11.17] / -0.16	-0.09 [-0.23 to 0.05] / -0.05

Table 4. Comparison of the arterial oxygenation, venous oxygenation, oxygen extraction fraction, cerebral blood flow, and cerebral metabolic rate of oxygen obtained from this study with that of previous reports. CBF = cerebral blood flow; CMRO2 = cerebral metabolic rate of oxygen; CSvO2 = cerebral venous oxygen saturation; CSaO2 = cerebral arterial oxygen saturation; OEF = oxygen extraction fraction; Hct = hematocrit ^*^Median and interquartile range reported.

Study	Method	Number of Subjects	PMA (weeks)	CSaO2 (%)	CSvO2 (%)	OEF (%)	CBF (mL/100g/min)	CMRO2 (µmol/100g/min)
This study	MRI	19 preterm at term	40.4 ± 1.4	98.3 ± 1.5	63.9 ± 4	34.9 ± 4.3	14.3 ± 4.2	29.5 ± 8.6
Altman et al., (1993) (Altman et al. 1993)	PET	11 HIE and other conditions	35.1±6.2	N/A	21.6±21.0	16.06±13.2	21.6±21.1	21.4±16.4
De Vis et al., (2014) (De Vis et al. 2014)	MRI	10 preterm at term	39	97±1	52±12	49±12	14±3	30±6
		9 HIE	38	96±3	65±13	32±12	12±4	24±12
Liu et al., (2014) (Liu et al. 2014)	MRI	12 healthy	37.4±2.9	95.8±2.2	62.6±8.3	N/A	13.4±4.2	38.3±17.7
Elwell et al., (2005) (Elwell et al. 2005)	NIRS	9 ventilatory support	29.2±5.3	N/A	N/A	N/A	N/A	45.9±12.3
Skov et al., (1993) (Skov et al. 1993)	NIRS	10 asphyxiated (full term)	38.8±1.9	94±7	67.3±9.2	28.4±0.3	36.5±17.9	62.6±35.8
		22 Respiratory Distress Syndrome (RDS) (preterm)	29.8±2.9	96.5±5	53.4±15.4	44.6±2.1	11.9±5.2	44.7±17.9
Yoxall & Weindling, (1998) (Yoxall and Weindling 1998)	NIRS	9 ventilatory support	23-37	N/A	62.6±8.3	N/A	13.4±4.2	38.3±17.7
Qi et al, (2018) (Qi et al. 2018)*	MRI	38 healthy	35.71 (5.36)	95 (2)	63.85 (4.8)	32.35 (6.26)	15.35 (9.13)	38.09 (18.84)
		23 Punctate White Matter Lesions (PWML)	35.14 (3.29)	95 (2)	68.7 (16.3)	27.53 (18.94)	12.63 (7.83)	29.11 (16.8)