The Application of Magnetic Susceptibility Separation for Measuring Cerebral Oxygenation in Preterm Neonates

Thomas Gavin Carmichael1,2, Alexander Rauscher3, Ruth E Grunau2,3, and Alexander Mark Weber2,3,✉

2024-10-02

Abstract

**Background**: Quantitative susceptibility mapping (QSM) is a magnetic resonance imaging (MRI) modality proposed to be a viable method of measuring cerebral oxygenation in neonates given its sensitivity to deoxyhemoglobin, a paramagnetic molecule. During QSM, however, paramagnetic sources can be obscured by opposing diamagnetic sources such as water and myelin. We sought to evaluate whether QSM images alone, or an algorithm that attempts to isolate their paramagnetic components, are more accurate in measuring oxygenation of the major cerebral veins in a cohort of neonates born preterm. Additionally, we aimed to determine whether a difference in oxygenation existed between the major cerebral veins.

**Methods**: 19 neonates born preterm were scanned on a 3T research MRI at term equivalent age. The protocol included a multi-echo susceptibility-weighted imaging sequence. The acquired imaging data were processed as QSM images to obtain the susceptibility values of the superior sagittal sinus (SSS) and central cerebral veins (CCV). These values were used to calculate the oxygen saturation (SvO2) of the SSS and CCV. QSM images were subsequently processed to isolate their paramagnetic components. SvO2 values of the SSS and CCV were calculated again from the paramagnetic components.

**Results**: The mean SvO2 values of the SSS and CCV calculated from QSM images were found to be 72.4% (SD, 3.4%) and 68.7% (SD, 3.5%), respectively. The mean SvO2 values calculated from paramagnetic components were found to be 58.1% (SD, 7.3%) for the SSS and 57.7% (SD, 7.0%) for the CCV.

**Conclusion**: SSS SvO2 values derived from paramagnetic components agreed well with the existing literature and were closer than the values derived from QSM, however, they displayed greater variability. Although the CCV SvO2 data from QSM aligns more closely with existing literature, it is important to note that the current literature on this topic remains relatively limited in the CCV. Thus, decomposing QSM images into paramagnetic components shows great promise as a method for more accurately measuring cerebral oxygenation in neonates but may require more research to improve precision. Notably, no significant difference in oxygenation was observed between the CCV and the SSS, contrasting with previous studies.

1 The University of British Columbia  
2 The University of British Columbia  
3 The University of British Columbia

✉ Correspondence: [Alexander Mark Weber <aweber@bcchr.ca>](mailto:aweber@bcchr.ca)

## Acknowledgments

We wish to acknowledge the work of and thank Victoria Tapics (Research Nurse); Vicki Goh (Research Nurse); Chacko Anil (Neonatologist); and Michael A. Sargent (Radiologist).

## Funding

Authors AMW and REG were co-primary applicants for a BC Children’s Hospital Research Institute - Brain, Behaviour and Development Catalyst Grant ($20,000). AMW was supported by an establishment award from BCCHRI. Scanning was partly funded through a special award to AMW from BCCHRI .

# Introduction

With advances in neonatal medical care, more infants born preterm are surviving into childhood (McKenzie, Lynch, and Msall 2022). These children are at high risk of acquiring adverse neurodevelopmental outcomes when compared to their term-born peers (Twilhaar et al. 2018). Irregularities in early cerebral oxygen levels have been identified as a potential source of such delays, where too little oxygen provided during NICU care can result in white matter injury, while too much oxygen can result in reduced cortical connectivity (Rantakari et al. 2021). As such, being able to precisely, accurately, and non-invasively measure cerebral oxygenation is necessary for understanding and improving neurodevelopmental outcomes in preterm neonates.

Unfortunately, there exist many challenges in measuring cerebral oxygen metabolism in neonates. Cerebral metabolic rate of oxygen (CMRO2) using oxygen-15 positron emission tomography (PET) (Mintun et al. 1984), has been measured in infants (Altman et al. 1988), and is considered the gold standard. However, this method is invasive, requiring ionizing radiation, which limits its suitability for neonates. A less invasive option for evaluating brain hemodynamics is near-infrared spectroscopy (NIRS), which uses the attenuation of near-infrared light (~650–950 nm) as it passes through biological tissue (Skov et al. 1993). Deoxygenated and oxygenated hemoglobin absorb this light differently, allowing NIRS to estimate changes in deoxyhemoglobin and oxyhemoglobin (Wray et al. 1988) and thus provide an estimate of cerebral venous oxygen saturation (SvO2). While NIRS offers the advantage of being non-invasive and continuous bedside monitoring, it is limited to regional assessments where the probe is placed and is sensitive only to superficial brain tissue due to the shallow penetration depth of near-infrared light (Boas, Dale, and Franceschini 2004).

For the preceding reasons, non-invasive MRI-based techniques are actively being explored to assess whole-brain oxygenation. MRI based methods have been developed for adults (Jain et al. 2011; Lu and Ge 2008; Xu, Ge, and Lu 2009) and are only beginning to be explored in neonates (De Vis et al. 2014; Liu et al. 2014; Qi et al. 2018; Jain et al. 2011; Jiang et al. 2019). One limitation of these methods, however, is the fact that SvO2 is often measured using a single imaging slice, averaging values across several voxels in the superior sagitall sinus (SSS). An alternative MRI method using quantiative susceptibility mapping (QSM) has been proposed, which measured SvO2 across the whole-brain. However, this method left room for improvement, as it removed the SSS, and required an arbitraty threshold value of 0.15 ppm in order to acquire realistic results (Weber et al. 2021).

In the present study, we set out to determine whether decomposing the QSM image into its paramagnetic and diamagnetic comoponents would allow for a more accurate assessment of SvO2 in the central cerebral veins (CCV) of a cohort of preterm neonates. We also had a secondary aim of preserving the SSS vessel in our QSM images and using this data to determine whether a difference in oxygenation existed between the SSS and the CCV.

# Methods

The study was approved by the Clinical Research Ethics Board at the University of British Columbia and Children’s & Women’s Hospital (H21-00655) and written informed consent was obtained from the parent/guardian for each infant.

## Study population

Participant data comes from a previous study \*\*\* . Participants consisted of preterm neonates born between 25- and 31-weeks gestational age (GA) who were admitted to the level III NICU at BC Women’s Hospital. Recruitment took place over a span of one year, from February 2021 to January 2022, facilitated by a dedicated research nurse. Parents of eligible infants were approached by the research nurse prior to discharge from the NICU to explain the study objectives and seek their consent for participation. Infants meeting the criteria for inclusion were scanned for the study if they had already been discharged from the NICU, were in stable condition, and had reached a term equivalent age of 37 to 44 weeks GA. However, certain exclusion criteria were applied to ensure the homogeneity and integrity of the study sample: Infants were excluded if there was clinical evidence of a congenital malformation or syndrome, a TORCH infection, or ultrasound evidence of large parenchymal hemorrhagic infarction (>2 cm, Grade 4 intraventricular hemorrhage).

## Image acquisition

MR imaging was performed on a 3.0 Tesla General Electric Discovery MR750 scanner (scanner software version DV26.0\_R03) equipped with a SREE Medical Systems single-channel neonatal head coil ([Table 1](#tbl-mri)). The scans were conducted at the BC Children’s MRI Research Facility. Prior to the scanning procedure, subjects were carefully prepared by a research nurse. Swaddling and feeding were used to ensure the comfort and cooperation of the subjects during the scan. Importantly, no sedatives or invasive markers were utilized throughout the procedure. Subjects were placed within a specially designed SREE Medical Systems MRI compatible incubator, which facilitated both safety and motion minimization. Molded foam was strategically positioned around the head and body within the incubator to further restrict subject movement. To protect against potential hearing damage, ear plugs were employed during the scanning process. Additionally, a pulse oximeter was affixed to the subject’s foot to monitor arterial oxygen saturation and heart rate throughout the scan.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Table** 1**.** **Technical parameters for MR imaging pulse sequences** | | | | |
|  | T1w | T2w | pcASL | SWI |
| Sequence | 3D FSPGR | 3D CUBE | Multi-shot 3D fast spin-echo | 3D spoiled GRE flow-compensated |
| Phase-encoding direction | Coronal | Sagittal | Axial | Axial |
| TR (ms) | 7.74 | 2,300 | 4,680 | 30.9 |
| TE (ms) | 2.97 | 66.29 | 10.55 | 5.24 |
| Flip angle | 12° | 90° | 111° | 20° |
| FOV (cm) | 20 | 20 | 24 | 25 |
| Acquisition matrix | 512 x 512 | 256 x 256 | 128 x 128 | 256 x 256 |
| In-plane resolution (mm) | 0.39 x 0.39 | 0.78 x 0.78 | 1.875 x 1.875 | 0.977 x 0.977 |
| Slice thickness (mm) | 1 | 1 | 4 | 2, reconstructed to 1 with zero filling (ZIP2) |
| Number of slices | 126 | 106 | 50 | 92 |
| Additional parameters | n/a | n/a | 1,450 ms label period; 2,025 ms pulse label; 24 control-label pairs | n/a |
| Scan duration | 4 min 39 s | 5 min 1 s | 5 min 26 s | 5 min 29 s |
| T1w = T1-weighted; T2w = T2-weighted; pcASL = pseudo-continuous arterial spin labelling; SWI = susceptibility weighted imaging; FSPG = fast spoiled gradient echo; CUBE = General Electric name of sequence, not an acronym; GRE = gradient echo; ZIP2 = through-plane zero filling interpolation | | | | |

The MRI scan protocol comprised of the following sequences: a T1-weighted scan, a T2-weighted scan, a pseudo-continuous arterial spin labeling (ASL) scan, a multi-echo susceptibility-weighted imaging scan, and a diffusion-weighted imaging (DWI) spin-echo echo planar imaging (EPI) sequence. The DWI sequence was not used for the present study.

## Image analysis

The raw DICOM files acquired from the scanning procedure were converted to NIfTI (Neuroimaging Informatics Technology Initiative) format using Chris Rorden’s dcmniix tool (X. Li et al. 2016). SWI magnitude data files were then used to create subject-specific brain masks that would not erode the SSS during QSM processing, an issue faced by our group in the past \*\*\* . A step-by-step summary of the pipeline used is shown in [Figure 1](#fig-graph).

|  |
| --- |
| **Figure** 1**.** Pipeline for generating subject-specific brain masks that include the superior sagittal sinus (SSS). Initial steps involved (1) creating brain a mask from the magnitude of the fifth echo of the susceptibility weighted scan. Subsequently, the brain mask is dilated and then (2) utilized in conjunction with a quantitative susceptibility mapping (QSM) script to generate a preliminary QSM image. Further refinement involved (3) segmenting the SSS from the QSM image manually to create a tissue mask of the SSS region. Finally, (4) the vascular mask of the SSS is integrated with the initial brain mask, forming the comprehensive brain mask essential for obtaining susceptibility data that includes the SSS. |

First, the fifth echo SWI magnitude file was processed using FSL’s (v. 6.0.7.3) (Woolrich et al. 2009) fslroi, fslmaths, and bet (Smith 2002) to create a preliminary brain mask, similar to our previous efforts, which does not contain the SSS. Fslroi was used to isolate the fifth echo of the magnitude data, which was then squared using fslmaths and the option -sqr. Squaring the magnitude image was found to dramatically improve subsequent brain extraction. The resulting image was then used to create the preliminary brain mask using bet with the options -m and -R. The former flag generated a binary brain mask, while the latter performed a more robust brain centre estimation. The brain mask was then dilated by 7 voxels using fslmaths and the options -kernel boxv and -dilM in order for the dilated mask to contain the SSS (along with unwanted tissue as well). This mask was then used, along with the phase images, in a MATLAB script for QSM calculation from Christian Kames (Kames, Wiggermann, and Rauscher 2018) to produce a preliminary QSM image that contained the SSS, albeit with fairly low signal-to-noise ratio and other unwanted tissue. Given the high contrast in voxel intensity between the SSS and surrounding tissue, the select by intensity tool in FSLeyes (McCarthy 2023) was then used to segment the SSS from the QSM image and create a 3D mask of the selected region. Using fslmaths and the options -add and -bin, the SSS mask was then combined with the original brain mask of the fifth echo. This resulted in a brain mask that contained only brain and SSS signal. Finally, this mask was used in a final QSM post-processing step to create a QSM image that includes the SSS while maintaining a high signal-to-noise ratio, making it suitable to obtain accurate susceptibility values.

STI Suite (v. 3.0) (W. Li et al. 2014), was used to process the final QSM images as it produced the cleanest images without eroding the SSS. The finalized brain mask and the last three echoes of the magnitude and phase images were used in STI Suite along with the following parameters: 0.9766 x 0.9766 x 1 mm3 voxel size, 5 ms TE1, 5.3 ms TE, and 77.4 ms sum TE, B0 strength = 3, and B0 direction = [0, 0, 1]. The 3D GRE data option was selected for the phase processing stage, and STAR-QSM was selected for the QSM stage. Finally, the `select by intensity’ tool in FSLeyes was then used to semi-automatically make vascular masks of the SSS and CCV from each subject’s QSM image. The vascular masks were used to calculate the mean susceptibility of each subject’s SSS and CCV from their QSM image with fslstats.

To isolate the paramagnetic component of subjects’ QSM data, the -separation toolbox (Shin et al. 2021) from the Laboratory for Imaging Science and Technology was used. Each subject’s magnitude and phase SWI data were used along with the following parameters: 0.9766 x 0.9766 x 1 mm3 voxel size; TE (s) = [0.005, 0.0102, 0.0155, 0.0207, 0.026]; delta TE (s) = 0.0052; B0 strength = 3; B0 direction = [0, 0, 1]. The mean susceptibility of each subject’s SSS and CCV in their paramagnetic maps was calculated with the same vascular masks used for the QSM images. Sample images showing the magnitude, final QSM, and final paramagnetic component images are shown in [Figure 2](#fig-sample).

|  |
| --- |
| **Figure** 2**.** An example of subject imaging data. A sample sagittal, coronal, and axial slice is displayed for each image. (a) The 1st echo of the magnitude susceptibility weighted imaging sequence; (b) the final quantitative susceptibility mapping image; and (c) the paramagnetic component isolated from the quantitative susceptibility map. The bars in (b) and (c) indicates the range of susceptibility values. |

Once the mean susceptibility values of the SSS and CCV were obtained from the subjects’ QSM images and paramagnetic maps, venous oxygen saturation (SvO2) was calculated with the following equation (Berg et al. 2021):

where is the vessel’s measured susceptibility, is the constant representing the susceptibility changes of oxygenated blood relation to water, is the difference in susceptibility between oxygenated and deoxygenated blood, and Hct is the subject’s hematocrit. was -0.21 \* 4 ppm as per Portnoy et al. (2018) and (Sedlacik, Rauscher, and Reichenbach 2007), while was -0.03 \* 4 ppm as per (Weisskoff and Kiihne 1992). Subjects’ Hct for the day of the scan was calculated using a four-parameter Weibull function with previously measured values while still in the NICU.

## Statistical analysis

Statistical analysis was performed using R and RStudio (v. 2023.09.1 Build 494) (R Core Team 2022; RStudio Team, n.d.). Mean and standard deviation values are reported for most statistics, unless specified otherwise. A paired Student’s t-test was used to determine statistical significance (p <0.05) between two parameters (e.g.  values between venous structures).

# Results

A total sample size of 19 infants were scanned, with a mean ( standard deviation) gestational age of 28.8 1.68 weeks and a mean birth weight of 1276.05 294.87 grams. A comprehensive summary of neonatal characteristics, including additional demographic and clinical data, is provided in [Table 2](#tbl-dem) for reference.

|  |  |
| --- | --- |
| **Table** 2**.** **Demographic and clinical characteristic of the study sample.** | |
| Variable | Subject data (n = 19) |
| Gestational age, weeks (mean ± SD) | 28.8 ± 1.68 |
| Corrected gestational age on scan day, weeks (mean ± SD) | 40.36 ± 1.4 |
| Number of male neonates (%) | 10 (52.63) |
| Birth weight, g (mean ± SD) | 1276.05 ± 294.87 |
| Weight on scan day, g (mean ± SD) | 3396.58 ± 597.72 |
| Days spent in NICU (median, IQR) | 53, 23 |
| Days on ventilation (median, IQR) | 31, 28.5 |
| SD = standard deviation; IQR = inter quartile range | |

The mean SvO2 values for the SSS and the CCV were found to be 0.72 0.03 and 0.69 0.03 ppm, respectively, when determined from the QSM data. When determined from the paramagnetic map, the mean SvO2 values for the SSS and the CCV were found to be 0.58 0.07 %, respectively. A summary of the measured physiological parameters, including the chi values used to calculate SvO2, can found in [Table 3](#tbl-chistats).

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Table** 3**.** **Summary of acquired physiological parameters.** Mean SD is shown for chi and SvO2 values. The P-value and 95% confidence interval (CI) were obtained through the comparison of values between QSM and paramagnetic maps; (n=19). | | | | | |
| Region | Measure | QSM | Paramagnetic map | p-value | 95% CI |
| SSS | Chi (ppm) | 0.1 ± 0.02 | 0.21 ± 0.05 | 2.84e-11 | -0.13, -0.09 |
| SSS | SvO₂ (%) | 72.46 ± 3.43 | 58.14 ± 7.3 | 6.12e-10 | 0.12, 0.17 |
| CCV | Chi (ppm) | 0.13 ± 0.02 | 0.22 ± 0.05 | 6.25e-09 | -0.1, -0.07 |
| CCV | SvO₂ (%) | 68.71 ± 3.46 | 57.69 ± 6.97 | 2.16e-09 | 0.09, 0.13 |
| QSM = quantitative susceptibility mapping; CI = confidence interval; SSS = superior sagitall sinus; CCV = central cerebral vein | | | | | |

Region-specific and SvO2 values acquired from QSM were compared to values acquired from paramagnetic maps. In both the SSS and CCV, it was found that a significant difference existed between values acquired ( and SvO2) from QSM and paramagnetic maps (p < 0.05). A boxplot showing the comparisons made is shown in [Figure 3](#fig-methodplot).

|  |
| --- |
| **Figure** 3**.** Vein-specific susceptibility and oxygen saturation values by method. (A, B) contains violin plots comparing subject χ (ppm) acquired from QSM (A) and its paramagnetic component (B); (C, D) contains violin plots comparing subject SvO2 (%) acquired from QSM (C) and its paramagnetic component (D). Raw data points from paramagnetic maps are shown as filled green circles and raw data points from QSM are shown as filled orange circles. Each line connects the raw data points of a single subject. (\*\*\*) indicates P<0.05. |

The acquired and SvO2 values were additionally compared between veins. In data created from QSM, a significant difference was found between the CCV and SSS in mean (p < 0.05; 95% CI [0.017, 0.04]) and mean SvO2 (p < 0.05; 95% CI [-0.052, -0.023]). In data acquired from paramagnetic maps, no significant difference was observed between the CCV and the SSS in either mean (p = 0.711; 95% CI [-0.02, 0.029]) or mean SvO2 (p = 0.752; 95% CI [-0.034, 0.029]). A summary of these comparisons is represented in [Figure 4](#fig-regionplot).

|  |
| --- |
| **Figure** 4**.** Inter-venous comparisons of susceptibility and oxygen saturation. Violin plots comparing (A, C) χ (ppm) and (B, D) SvO2 (%) between the CCV and the SSS. Panels (A) and (B) used data acquired from QSM, and its raw data points are shown as filled orange circles. Panels (C) and (D) used data acquired from paramagnetic maps, and its raw data points are shown as filled green circles. Each line connects the raw data points of a single subject. (\*\*\*) indicates p<0.05; (n.s.) indicates no significant difference. |

# Discussion

The primary objective of the present study was to assess whether the application of magnetic susceptibility separation to neonatal QSM data could provide more accurate SvO2 measurements without the need for an arbitrary threshold value. To the best of our knowledge, we are the first to test this in a neonatal cohort, as susceptibility separation has been typically evaluated as a method of imaging myelin and brain iron in adult subjects (Shin et al. 2021; Ahmed et al. 2023). Our results showed that the SvO2 values of the SSS and CCV obtained from susceptibility separation are significantly lower than the respective SvO2 values obtained from QSM alone. When our results were compared to the literature, we found that our SSS SvO2 data from susceptibility separation agreed well with the findings of other studies measuring SvO2 of the SSS in similar subject populations. Conversely, the paramagnetic CCV SvO2 data saw less agreement with the existing literature than the corresponding data from QSM. However, there is reason to believe our paramagnetic CCV values may be accurate given their similarity to the paramagnetic SSS values and the limitations of the two studies that observed CCV SvO2. Additionally, it is important to note that our SvO2 measurements from susceptibility separation had greater variance than our measurements from QSM, indicating a limitation that should be addressed in future research. Overall, the present work demonstrates the promise of susceptibility separation as an MRI post-processing technique that can measure the oxygenation of the cerebral veins of infant subjects, a useful marker of regional oxygen consumption in the brain.

## Comparison with literature values

To evaluate the validity of our results, we compared the mean SvO2 values we obtained through QSM and susceptibility separation to the mean SvO2 values found by MRI studies investigating the oxygenation of the SSS or the CCV. Notably, the number of studies that measure the SvO2 of the CCV, or any of its individual veins, in infants is fairly lower than the number of studies investigating the oxygenation of the SSS. Our comparison is summarized in [Table 4](#tbl-litvalues).

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Table** 4**.** **Cerebral oxygenation values of neonates and fetuses in the literature.** | | | | |
| Region | Study | Subjects | Method | SvO~2~ (\%) |
| Whole-brain | Skov et al. (1993) | Preterm neonates (n=9) | NIRS | 53.4 ± 15.4 |
| Whole-brain | Skov et al. (1993) | Asphyxiated term neonates (n=10) | NIRS | 67.3 ± 9.4 |
| Whole-brain | Altman et al. (1993) | Preterm and term neonates with HIE (n=11) | PET | 21.6 ± 21.0 |
| SSS | Gou et al. (2024) | Healthy neonates (n=37) | MRI: TRUST | 66.7 ± 4.9 |
| SSS | Jiang et al. (2019) | Healthy neonates (n=4) | MRI: aTRUPC | 64.8 ± 2.9 |
| SSS | De Vis et al. (2014) | PT-TEA eonates (n=18) | MRI: T2-TRIR | 52.0 ± 12.0 |
| SSS | Yadav et al. (2020) | Late third trimester fetuses (n=33) | MRI: Susceptometry | 58.6 ± 4.8 |
| SSS | \textbf{This study} | PT-TEA neonates n=19 | MRI: QSM | 72.5 ± 3.4 |
| SSS | \textbf{This study} | PT-TEA neonates n=19 | MRI: $\chi$-separation | 58.1 ± 7.3 |
| CCV | Weber et al. (2021) | Preterm neonates with HIE (n=8) | MRI: QSM | 72.2 ± 6.0 |
| CCV | Weber et al. (2021) | Healthy neonates (n=8) | MRI: QSM | 73.6 ± 2.8 |
| CCV | Jiang et al. (2019) | Healthy neonates (n=4) | MRI: aTRUPC | 70.2 ± 3.3 |
| CCV | \textbf{This study} | PT-TEA neonates n=19 | MRI: QSM | 68.7 ± 3.5 |
| CCV | \textbf{This study} | PT-TEA neonates n=19 | MRI: $\chi$-separation | 57.7 ± 7.0 |
| PT-TEA = born preterm and scanned at term-equivalent age; late third trimester = >35 weeks gestational age; HIE = hypoxic-ischemic encephalopathy; TRUST = T2-relaxation-under-spin tagging; aTRUPC = accelerated T2-relaxation-under-phase-contrast; T2-TRIR = T2-tissue-relaxation-inversion-recovery; SWI = susceptibility weighted imaging. | | | | |

As shown in [Table 4](#tbl-litvalues), the infants observed in MRI studies investigating cerebral vein oxygenation noticeably differ in clinical status, with three studies involving healthy neonates (Weber et al. 2021; Gou et al. 2024; Jiang et al. 2019), three studies (including the present study) involving preterm neonates (Weber et al. 2021; De Vis et al. 2014), and one study involving late third trimester fetuses (Portnoy et al. 2018). In the studies involving healthy neonates, the SvO2 of the SSS fell within the range of 64.8% – 66.6% (Gou et al. 2024; Jiang et al. 2019), while the SvO2 of the CCV fell within the range of 70.2% - 73.6% (Weber et al. 2021; Jiang et al. 2019). Notably, the SvO2 value of the SSS we obtained from susceptibility separation (58.1%) was closest to values obtained from the studies involving late third trimester fetuses (Yadav et al. 2018) or pre-term neonates (De Vis et al. 2014), each finding an SSS SvO2 value of 58.6% and 52.0%, respectively. It is important to note the difference in MRI modalities used to obtain these values. For their study, Yadav et al. (2018) used MR susceptometry, which involves measuring the difference in phase between the chosen vessel and its background in imaging data from an SWI scanning sequence (Yadav et al. 2018). In De Vis et al. (2014), the authors used T2-TRIR, which allowed them to determine the transverse relaxation rate of blood within the vessel, which can be used alongside hematocrit data to estimate SvO2. Additionally, the GA of infants scanned in our study ranged between 37 and 44 weeks, while the GA of the fetuses scanned in Yadav et al. (2018) was ≥35 weeks and the GA of infants scanned in De Vis et al. (2014) ranged between 38 and 40 weeks. As such, our SSS SvO2 values found through susceptibility separation show promise given their similarity to the SvO2 values found by Yadav et al. (2018) and De Vis et al. (2014), two studies that involved comparable subject populations and used considerably different methods.

Conversely, the SvO2 value of the CCV we obtained through QSM (68.7%) was closest to values from similar studies in the literature. In Weber et al. (2021), QSM was used to measure an SvO2 of 71.5% in preterm neonates with HIE and an SvO2 of 73.6% in healthy neonates. In their study, Jiang et al. (2019) also involved healthy neonates and obtained an SvO2 of 70.2% through an accelerated TRUPC sequence. In contrast, the SvO2 of the CCV found through susceptibility separation was 57.7%. This disparity from the literature, however, may not undermine the value we obtained, as the study design of Weber et al. (2021) and Jiang et al. (2019) may prevent their values from being representative of the study demographic. In Weber et al. (2021), the authors utilized an arbitrary 0.15 ppm threshold and included all values above 0.15 when measuring the mean of the CCV, which potentially led to the introduction of from veins outside the CCV. In Jiang et al. (2019), the authors acquired their data from 4 subjects, a notably small sample size. Given the limitations of the existing literature and the similarity of the mean paramagnetic CCV SvO2 value (57.7%) to the mean paramagnetic SSS SvO2 value (58.1%), it is plausible that susceptibility separation provides accurate measurements of oxygenation in both cortical and subcortical veins.

Another notable distinction between our findings and those of the existing literature was that we observed no significant oxygenation difference between the SSS and the CCV when was derived from paramagnetic maps. Jiang et al. (2019), the only other study that also measured SvO2 in both the SSS and CCV, observed significantly lower oxygenation in the SSS (64.8%) when compared to the CCV (70.2%). Given the small sample size utilized by Jiang et al. (2019), it is difficult to ascertain whether this is generalizable to all neonates.

## Limitations and future directions

This study has a few limitations that should be considered for future research. Firstly, only 19 infants were recruited for scanning. Given the emotional toll placed on parents when their child is born preterm, it is understandable that they may show reluctance in consenting to further testing that is not medically necessary. Obtaining a larger sample size in future studies, however, may provide greater insight into the efficacy of susceptibility separation. Secondly, this study did not include healthy neonates born at term, resulting in a lack of a control cohort. The addition of such a group may provide further validity to any findings and may reveal potential differences in cerebral oxygen consumption between term and preterm neonates. Finally, future studies should consider the use of multi-echo T2 imaging data when performing the decomposition of QSM images. The toolbox applied by this study for QSM decomposition (Shin et al. 2021) utilizes R2 data, which can be obtained from multi-echo T2 imaging. Our study protocol involved the collection of multi-echo SWI imaging data, and as such, we could only use R2^\*^ data to perform the decomposition. Furthermore, this may account for the reduced precision of SvO2 values obtained through susceptibility separation.

# Conclusion

This study aimed to evaluate how the use of susceptibility separation on preterm neonatal QSM images in order to provide greater accuracy in determining the oxygenation of cerebral venous vessels. We compared venous specific SvO2 values obtained from QSM images and their respective paramagnetic components to SvO2 values from neonatal MRI studies. We found that susceptibility separation provided SvO2 values of the SSS that were comparable to values found in the literature, providing evidence that this processing technique may be a valid tool for measuring regional cerebral oxygen consumption. Additionally, we were able to simultaneously measure SvO2 in both the SSS and CCV, which permitted us to observe no difference in oxygenation between the two vessels when considering data from isolated paramagnetic components. Ultimately, we hope our work inspires future studies that seek to explore and improve the capabilities of magnetic susceptibility separation, culminating in the development of a tool for clinicians and researchers alike.

# References

Ahmed, Maruf, Jingjia Chen, Arvin Arani, Matthew L. Senjem, Petrice M. Cogswell, Clifford R. Jack, and Chunlei Liu. 2023. “The Diamagnetic Component Map from Quantitative Susceptibility Mapping (QSM) Source Separation Reveals Pathological Alteration in Alzheimer’s Disease-Driven Neurodegeneration.” *NeuroImage* 280 (October): 120357. <https://doi.org/10.1016/j.neuroimage.2023.120357>.

Altman, Denis I., William J. Powers, Jeffrey M. Perlman, Peter Herscovitch, Sara L. Volpe, and Joseptemberh J. Volpe. 1988. “Cerebral Blood Flow Requirement for Brain Viability in Newborn Infants Is Lower Than in Adults.” *Annals of Neurology* 24 (2): 218–26. <https://doi.org/10.1002/ana.410240208>.

Berg, Ronja C., Christine Preibisch, David L. Thomas, Karin Shmueli, and Emma Biondetti. 2021. “Investigating the Effect of Flow Compensation and Quantitative Susceptibility Mapping Method on the Accuracy of Venous Susceptibility Measurement.” bioRxiv. <https://doi.org/10.1101/2021.04.14.439812>.

Boas, David A., Anders M. Dale, and Maria Angela Franceschini. 2004. “Diffuse Optical Imaging of Brain Activation: Approaches to Optimizing Image Sensitivity, Resolution, and Accuracy.” *NeuroImage*, Mathematics in Brain Imaging, 23 (January): S275–88. <https://doi.org/10.1016/j.neuroimage.2004.07.011>.

De Vis, J. B., E. T. Petersen, T. Alderliesten, F. Groenendaal, L. S. de Vries, F. van Bel, M. J. N. L. Benders, and J. Hendrikse. 2014. “Non-Invasive MRI Measurements of Venous Oxygenation, Oxygen Extraction Fraction and Oxygen Consumption in Neonates.” *NeuroImage* 95 (July): 185–92. <https://doi.org/10.1016/j.neuroimage.2014.03.060>.

Gou, Yifan, W. Christopher Golden, Zixuan Lin, Jennifer Shepard, Aylin Tekes, Zhiyi Hu, Xin Li, et al. 2024. “Automatic Rejection Based on Tissue Signal (ARTS) for Motion-Corrected Quantification of Cerebral Venous Oxygenation in Neonates and Older Adults.” *Magnetic Resonance Imaging* 105 (January): 92–99. <https://doi.org/10.1016/j.mri.2023.11.008>.

Jain, Varsha, Michael C Langham, Thomas F Floyd, Gaurav Jain, Jeremy F Magland, and Felix W Wehrli. 2011. “Rapid Magnetic Resonance Measurement of Global Cerebral Metabolic Rate of Oxygen Consumption in Humans During Rest and Hypercapnia.” *Journal of Cerebral Blood Flow & Metabolism* 31 (7): 1504–12. <https://doi.org/10.1038/jcbfm.2011.34>.

Jiang, Dengrong, Hanzhang Lu, Charlamaine Parkinson, Pan Su, Zhiliang Wei, Li Pan, Aylin Tekes, Thierry A. G. M. Huisman, W. Christopher Golden, and Peiying Liu. 2019. “Vessel-Specific Quantification of Neonatal Cerebral Venous Oxygenation.” *Magnetic Resonance in Medicine* 82 (3): 1129–39. <https://doi.org/10.1002/mrm.27788>.

Kames, Christian, Vanessa Wiggermann, and Alexander Rauscher. 2018. “Rapid Two-Step Dipole Inversion for Susceptibility Mapping with Sparsity Priors.” *NeuroImage* 167 (February): 276–83. <https://doi.org/10.1016/j.neuroimage.2017.11.018>.

Li, Wei, Alexandru V. Avram, Bing Wu, Xue Xiao, and Chunlei Liu. 2014. “Integrated Laplacian-Based Phase Unwrapping and Background Phase Removal for Quantitative Susceptibility Mapping.” *NMR in Biomedicine* 27 (2): 219–27. <https://doi.org/10.1002/nbm.3056>.

Li, Xiangrui, Paul S. Morgan, John Ashburner, Jolinda Smith, and Christopher Rorden. 2016. “The First Step for Neuroimaging Data Analysis: DICOM to NIfTI Conversion.” *Journal of Neuroscience Methods* 264 (March): 47–56. <https://doi.org/10.1016/j.jneumeth.2016.03.001>.

Liu, Peiying, Hao Huang, Nancy Rollins, Lina F. Chalak, Tina Jeon, Cathy Halovanic, and Hanzhang Lu. 2014. “Quantitative Assessment of Global Cerebral Metabolic Rate of Oxygen (CMRO2) in Neonates Using MRI.” *NMR in Biomedicine* 27 (3): 332–40. <https://doi.org/10.1002/nbm.3067>.

Lu, Hanzhang, and Yulin Ge. 2008. “Quantitative Evaluation of Oxygenation in Venous Vessels Using T2-Relaxation-Under-Spin-Tagging MRI.” *Magnetic Resonance in Medicine* 60 (2): 357–63. <https://doi.org/10.1002/mrm.21627>.

McCarthy, Paul. 2023. “FSLeyes.” Zenodo. <https://doi.org/10.5281/zenodo.8376979>.

McKenzie, Kamryn, Emma Lynch, and Michael E. Msall. 2022. “Scaffolding Parenting and Health Development for Preterm Flourishing Across the Life Course.” *Pediatrics* 149 (Supplement 5): e2021053509K. <https://doi.org/10.1542/peds.2021-053509K>.

Mintun, M. A., M. E. Raichie, W. R. W. Martin, and P. Herscovitch. 1984. “Brain Oxygen Utilization Measured with O-15 Radiotracers and Positron Emission Tomography.” *Journal of Nuclear Medicine* 25 (2): 177–87.

Portnoy, Sharon, Natasha Milligan, Mike Seed, John G. Sled, and Christopher K. Macgowan. 2018. “Human Umbilical Cord Blood Relaxation Times and Susceptibility at 3 T: Human Umbilical Cord Blood Relaxation Times and Susceptibility at 3 T.” *Magnetic Resonance in Medicine* 79 (6): 3194–3206. <https://doi.org/10.1002/mrm.26978>.

Qi, Ying, Peiying Liu, Zixuan Lin, Hanzhang Lu, and Xiaoming Wang. 2018. “Hemodynamic and Metabolic Assessment of Neonates With Punctate White Matter Lesions Using Phase-Contrast MRI and T2-Relaxation-Under-Spin-Tagging (TRUST) MRI.” *Frontiers in Physiology* 9: 233. <https://doi.org/10.3389/fphys.2018.00233>.

R Core Team. 2022. “R: A Language and Environment for Statistical Computing.” Vienna, Austria: R Foundation for Statistical Computing.

Rantakari, Krista, Olli-Pekka Rinta-Koski, Marjo Metsäranta, Jaakko Hollmén, Simo Särkkä, Petri Rahkonen, Aulikki Lano, et al. 2021. “Early Oxygen Levels Contribute to Brain Injury in Extremely Preterm Infants.” *Pediatric Research* 90 (1): 131–39. <https://doi.org/10.1038/s41390-021-01460-3>.

RStudio Team. n.d. “RStudio: Integrated Development Environment for R.” Boston, MA: RStudio, PBC.

Sedlacik, Jan, Alexander Rauscher, and Jürgen R. Reichenbach. 2007. “Obtaining Blood Oxygenation Levels from MR Signal Behavior in the Presence of Single Venous Vessels.” *Magnetic Resonance in Medicine* 58 (5): 1035–44. <https://doi.org/10.1002/mrm.21283>.

Shin, Hyeong-Geol, Jingu Lee, Young Hyun Yun, Seong Ho Yoo, Jinhee Jang, Se-Hong Oh, Yoonho Nam, et al. 2021. “-Separation: Magnetic Susceptibility Source Separation Toward Iron and Myelin Mapping in the Brain.” *NeuroImage* 240 (October): 118371. <https://doi.org/10.1016/j.neuroimage.2021.118371>.

Skov, L., O. Pryds, G. Greisen, and H. Lou. 1993. “Estimation of Cerebral Venous Saturation in Newborn Infants by Near Infrared Spectroscopy.” *Pediatric Research* 33 (1): 52–55. <https://doi.org/10.1203/00006450-199301000-00011>.

Smith, Stephen M. 2002. “Fast Robust Automated Brain Extraction.” *Human Brain Mapping* 17 (3): 143–55. <https://doi.org/10.1002/hbm.10062>.

Twilhaar, E. Sabrina, Rebecca M. Wade, Jorrit F. De Kieviet, Johannes B. Van Goudoever, Ruurd M. Van Elburg, and Jaap Oosterlaan. 2018. “Cognitive Outcomes of Children Born Extremely or Very Preterm Since the 1990s and Associated Risk Factors: A Meta-analysis and Meta-regression.” *JAMA Pediatrics* 172 (4): 361. <https://doi.org/10.1001/jamapediatrics.2017.5323>.

Weber, A. M., Y. Zhang, C. Kames, and A. Rauscher. 2021. “Quantitative Susceptibility Mapping of Venous Vessels in Neonates with Perinatal Asphyxia.” *American Journal of Neuroradiology* 42 (7): 1327–33. <https://doi.org/10.3174/ajnr.A7086>.

Weisskoff, Robert M., and Suzanne Kiihne. 1992. “MRI Susceptometry: Image-based Measurement of Absolute Susceptibility of MR Contrast Agents and Human Blood: COMMUNICATIONS.” *Magnetic Resonance in Medicine* 24 (2): 375–83. <https://doi.org/10.1002/mrm.1910240219>.

Woolrich, Mark W., Saad Jbabdi, Brian Patenaude, Michael Chappell, Salima Makni, Timothy Behrens, Christian Beckmann, Mark Jenkinson, and Stephen M. Smith. 2009. “Bayesian Analysis of Neuroimaging Data in FSL.” *NeuroImage* 45 (1): S173–86. <https://doi.org/10.1016/j.neuroimage.2008.10.055>.

Wray, Susan, Mark Cope, David T. Delpy, John S. Wyatt, and E. Osmund R. Reynolds. 1988. “Characterization of the Near Infrared Absorption Spectra of Cytochrome *Aa3* and Haemoglobin for the Non-Invasive Monitoring of Cerebral Oxygenation.” *Biochimica Et Biophysica Acta (BBA) - Bioenergetics* 933 (1): 184–92. <https://doi.org/10.1016/0005-2728(88)90069-2>.

Xu, Feng, Yulin Ge, and Hanzhang Lu. 2009. “Noninvasive Quantification of Whole-Brain Cerebral Metabolic Rate of Oxygen (CMRO2) by MRI.” *Magnetic Resonance in Medicine* 62 (1): 141–48. <https://doi.org/10.1002/mrm.21994>.

Yadav, Brijesh Kumar, Uday Krishnamurthy, Sagar Buch, Pavan Jella, Edgar Hernandez-Andrade, Lami Yeo, Steven J. Korzeniewski, et al. 2018. “Imaging Putative Foetal Cerebral Blood Oxygenation Using Susceptibility Weighted Imaging (SWI).” *European Radiology* 28 (5): 1884–90. <https://doi.org/10.1007/s00330-017-5160-x>.