Evaluation of Neonatal Brain Myelination Using the T1- and T2-Weighted MRI Ratio

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Purpose: To validate the T1- and T2-weighted (T1w/T2w) MRI ratio technique in evaluating myelin in the neonatal brain.
Materials and Methods: T1w and T2w MR images of 10 term neonates with normal-appearing brain parenchyma were obtained from a single 1.5 Tesla MRI and retrospectively analyzed. T1w/T2w ratio images were created with a postprocessing pipeline and qualitatively compared with standard clinical sequences (T1w, T2w, and apparent diffusion coefficient [ADC]). Quantitative assessment was also performed to assess the ratio technique in detecting areas of known myelination (e.g., posterior limb of the internal capsule) and very low myelination (e.g., optic radiations) using linear regression analysis and the Michelson Contrast equation, a measure of luminance contrast intensity.
Results: The ratio image provided qualitative improvements in the ability to visualize regional variation in myelin content of neonates. Linear regression analysis demonstrated a significant inverse relationship between the ratio intensity values and ADC values in the posterior limb of the internal capsule and the optic radiations ($R^2 = 0.96$ and $P < 0.001$). The Michelson Contrast equation showed that contrast differences between these two regions for the ratio images were 1.6 times higher than T1w, 2.6 times higher than T2w, and 1.8 times higher than ADC (all $P < 0.001$). Finally, the ratio improved visualization of the corticospinal tract, one of the earliest myelinated pathways.
Conclusion: The T1w/T2w ratio accentuates contrast between myelinated and less myelinated structures and may enhance our diagnostic ability to detect myelination patterns in the neonatal brain.
Level of Evidence: 2
Technical Efficacy: Stage 2

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The assessment of normal neonatal myelin development can be challenging on routine MRI imaging, and subtle aberrations in myelination are difficult to detect because of the low intrinsic MRI contrast of the neonatal brain. Routine sequences such as FLAIR and diffusion-weighted imaging (DWI) can appear normal in infants with myelin-related insults such as hypoxic-ischemic injuries (HII) because of high water content in the infant brain.[1,2] This problem has been addressed with advanced MR imaging techniques that more directly assess myelination. For example, several studies have analyzed diffusion imaging to demonstrate that the general pattern of myelin development is associated with an overall reduction in diffusion and increase in anisotropy as the infant brain matures.[3–6] Advanced diffusion techniques such as diffusion kurtosis imaging have also been applied to examine differences in neonatal myelination in term and preterm infants, demonstrating kurtosis differences in myelinated and premyelinated regions.[7] Others have used magnetization transfer (MT) to measure the interaction of macromolecular and free protons after an off-resonance radiofrequency pulse, showing that the MT signal increases with myelination in the developing pediatric brain.[8]

Techniques such as multi-component driven equilibrium single pulse observation of T1 and T2 (mcDESPOT) can quantify myelin content with a myelin water fraction (MWF), taking advantage of different relaxation properties of free and bound water molecules. Deoni et al. applied mcDESPOT to infants age 3 to 11 months to provide the first quantitative in vivo assessment of myelin maturation.[9] While these techniques allow quantitative assessment of white matter, each has its limitations. DTI and MTR are only indirect markers of myelin, reflecting changes that may

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not necessarily be directly related to myelin content.[10] MWF is powerful in its quantitative information, but longer scan times make it less practical for use in pediatric populations.

Another approach for the assessment of myelination is the T1w/T2w ratio technique that accentuates the intrinsic contrast of myelin.[11] This ratio method uses superimposition of the contrasting properties of both T1 and T2 weightings. Glasser and Van Essen adopted this technique for mapping cortical cytoarchitecturally distinct regions.[11] Ganzetti et al have expanded upon this technique by developing normalization methods that allow for a more robust comparison of myelin content across subjects,[12] while others have evaluated intracortical myelin content across different ages using this method.[13,14]

The advantage of using the T1w/T2w ratio is that it increases the contrast-to-noise of white matter without increasing scan time. In addition, the T1w/T2w ratio can distinguish between highly myelinated and lightly myelinated cortical areas,[11] a finding that suggests this technique could be used to explore the spatial variation of myelin development in the neonatal brain. While previous studies focused on the variations of myelin in gray matter, there are limited studies that have applied this ratio technique to examine myelin variations in white matter, particularly in neonates.[11–15] The neonatal population is unique in that the T1 and T2 contrast is reversed relative to adults, with white matter demonstrating more hypointense signal relative to gray matter on T1w images and the opposite properties on T2w images.[16]

Moreover, the contrast between gray and white matter is severely reduced in neonates, making detection of subtle abnormalities particularly difficult. Liauw et al[17] demonstrated the utility of using a ratio method in infants by comparing T1w signal intensities of various brain regions to differentiate HII and myelination. Furthermore, Lee et al[15] applied the T1w/T2w ratio technique and found correlations between gestational age at time of scan and white matter regions of interest within the frontal lobes and corpus callosum.

In the current study, we used the T1w/T2w ratio technique to increase intrinsic myelin contrast on a voxel-wise, whole-brain basis in term neonates. The neonatal population has mostly unmyelinated brain with few but highly predictable areas of expected myelination, making this cohort an ideal population to test the efficacy of T1w/T2w ratio for visualizing changes related to myelin content in white matter. Our goal was to determine whether the T1w/T2w ratio provides better image contrast for detecting differences in myelination relative to routine T1w, T2w, or apparent diffusion coefficient (ADC) scans normally acquired in clinical imaging of neonates.

Materials and Methods

Subjects and Image Acquisition

This retrospective study was performed in accordance with Health Insurance Portability and Accountability Act regulations and was approved by the institutional review board. Informed consent was waived for all patients. All neonatal scans were performed on a single 1.5 Tesla (T) MRI scanner (Signa HDxt, GE Medical Systems) using a standard eight-channel head coil. These infants were all scanned using a "feed and wrap" strategy to minimize effects of motion, without the use of sedation. Six of the 10 subjects had volumetric T1w images obtained in the sagittal orientation, and four had two-dimensional (2D) T1w images. All 10 subjects had 2D T2w imaging. ADC images were obtained from DWI. DWI sequences were acquired with b values of 0 s/mm^2 and 1000 s/mm^2 applied in three orthogonal directions (x, y, z). Full details of MRI scan parameters are listed in the Supplementary Materials S1, which are available online. The routine clinical sequences (T1w, T2w, FLAIR, DWI, and susceptibility-weighted imaging) of 10 term neonates (mean gestational age = 38.7 weeks, 8 males, 2 females) that were interpreted as unremarkable with normal-appearing brain parenchyma on radiology report by a board-certified neuroradiologist were independently reviewed by a board-certified neuroradiologist (K.A.C., 8 years of experience) and a fourth-year radiology resident (J.E.S.) to determine whether any intraparenchymal abnormalities were present, such as infarct, hemorrhage, masses, or dysplasias. The mean age at time of scan was 4.7 days old. The birth demographics, clinical indications for scans, and neurological exam at time of imaging and at follow-up (if available) are listed in Table 1. The most common clinical indications were respiratory distress or possible seizure-like activity.

Myelination

Because myelin development is incomplete at term birth in normally developing infants, we use the term "myelination" in this study to refer to detectable myelin, as opposed to the completion of the myelin maturation process. For example, by term birth, the posterior limb of the internal capsule (PLIC) is known to be relatively highly myelinated compared with other structures, whereas the optic radiations have low levels of myelin based on imaging and histopathological studies.[10,16,18–21]

Postprocessing and Creation of T1w, T2w, ADC, and Ratio Images

The pipeline for postprocessing of T1w and T2w images is displayed in Figure 1. Using FSL (Oxford Centre for Functional MRI of the Brain Software Library; open source imaging analysis tools; http://fsl.fmrib.ox.ac.uk), T2w images were linearly registered to T1w images, and both T1w and T2w images were brain extracted and bias corrected.[22–25] Bias correction for T1w and T2w images was performed in FSL under the assumption that white matter voxels have approximately equal intensity, and any low frequency intensity changes are image artifacts.

In the neonate, this assumption is valid because most of the brain is unmyelinated. Highly myelinated regions such as the corticospinal tract are composed primarily of high frequency spatial components and thus have minimal effect on the bias estimation. All white matter partial volume maps created by the FSL bias

TABLE 1. Neonatal Demographics Demonstrating Gender, Gestational Age at Time of Delivery (in Weeks), Age at Time of Scan (in Days), Apgar Scores at 1 and 5 Minutes, Clinical Indications for Scans, and Clinical Neurological Exam at Time of Imaging and Follow-Up (If Available)

Subject	Gender	Gestational age at time of delivery (weeks)	Age at time of scan (days)	Apgar scores at 1 and 5 min	Clinical indication for scan	Clinical neurological exam
1	M	39 2/7	5	2, 6	Right subgaleal bleed and posterior subdural hematoma; neonatal seizures	Normal at time of imaging; Febrile seizures at 13 month follow-up; Normal brain MRI at 18 months
2	M	37 2/7	1	8,8	Transposition of great vessels	Normal at time of imaging and 3 month follow-up
3	F	36 6/7	12	9,9	Microcephaly, possible neonatal meningitis	Fever at time of imaging (meningitis); Normal at 12 month follow-up
4	M	38	6	9,9	Apnea, cyanosis	Normal at time of imaging and 1 month follow-up
5	M	40 5/7	0	4, 6	respiratory distress	Normal at time of imaging and 9 month follow-up
6	M	36	2	4, 9	Respiratory distress, ventricular septal defects,	Normal at time of imaging; seizures after post-cardiac surgery arrest at 21 months
7	M	40 3/7	1	9, 9	nystagmus, Cephalohematoma	Normal at time of imaging and 16 month follow-up
8	M	38	12	unknown	Possible seizure on EEG, cyanotic episode	Normal at time of imaging; no follow-up
9	M	40 1/7	3	7,8	Transposition of great vessels	Normal at time of imaging; no follow-up
10	F	40 1/7	5	9,9	Desaturation, possible nystagmus	Normal at time of imaging and 1 year follow-up

correction technique were visually inspected to confirm that they identified white matter regions.

To minimize the effect of differing sequences and scanning parameters on intensity scaling, an external calibration was applied to the bias corrected scans.[12] This intensity normalization step was performed for each subject using two masks of anatomical structures external to the brain, one with high T1w signal intensity and low T2w signal intensity and the other with the reverse properties. We chose the masseter muscle and vitreous humor of the eyeball for these masks because (a) these landmarks are easily visible in neonates and (b) they contain opposite signal properties at the extreme ends of the whole-brain intensity histogram.

This method is analogous to the method of Ganzetti et al with two exceptions: we used the masseter muscle instead of the temporalis muscle because the masseter was more easily visible on neonatal scans, and we used the mean voxel intensity value rather than the mode because we had fewer subjects.[12] The mean intensity value of each mask was obtained, and the following linear scaling equation was used for intensity normalization:

$$I_C = \left[\frac{\bar{E} - \bar{M}}{E - M}\right] \times I + \left[\frac{E\bar{M} - \bar{E}M}{E - M}\right]$$

where $\bar{A}$ and $\bar{M}$ are the mean intensity values of all the subjects' eye and muscle masks, respectively, and E and M are the mean intensity values of each subject's eye and muscle masks, respectively. I_C and I represent the calibrated and uncalibrated images.[12]

Using Advanced Normalization Tools (ANTs),[26] an open source medical image registration and segmentation software library that uses the Insight Toolkit (ITK) medical image processing library, we created a neonatal T1w template from our group of subjects and nonlinearly registered each subject's T1w and T2w image to this template using symmetric normalization (SyN), a diffeomorphic registration algorithm that uses spline interpolation (ANTs: http://stnava.github.io/ANTs/; ITK: https://itk.org). Once in template space, the final processed T1w image was divided by the T2w image to create a ratio image. The ADC images were processed using the same method as the T1w and T2w images, but

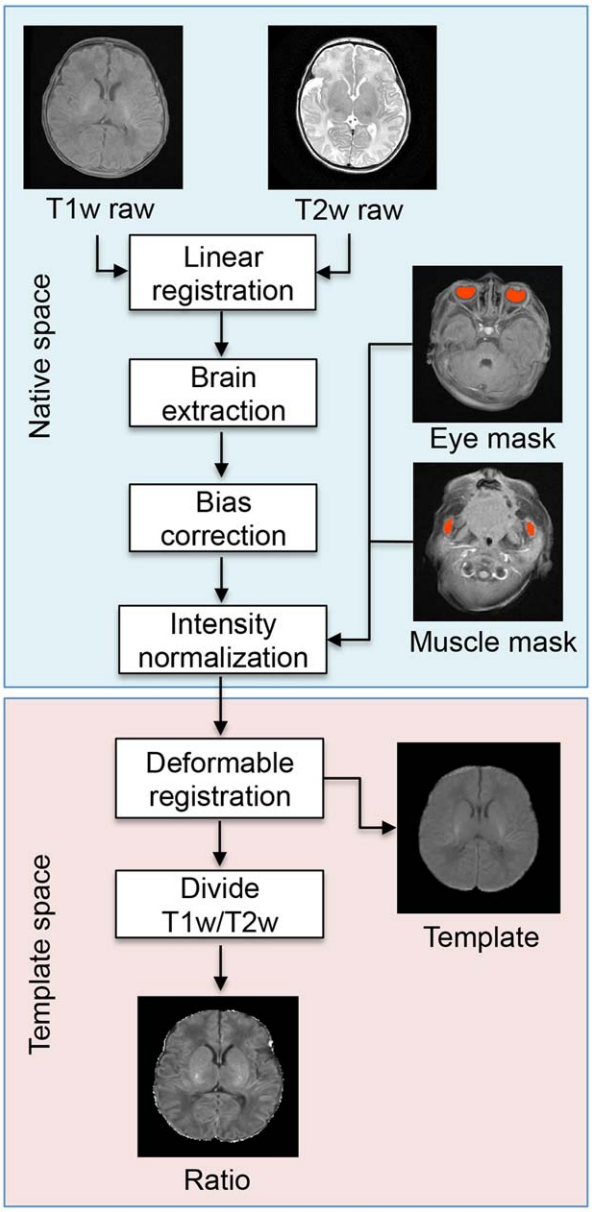

FIGURE 1: Pipeline for creating a T1w/T2w ratio image. This figure summarizes the key postprocessing steps, with representative images obtained from a single subject. The light blue box represents steps performed in native space, and the light red box represents steps performed in template space.

without intensity normalization. Thus, ADC images were linearly registered to T1w images, brain extracted, and bias corrected using FSL, and then images were nonlinearly registered to the neonatal template using ANTs.

Regions of interest (ROI) were manually drawn in the PLIC (84 mm^3) and optic radiations (316 mm^3) on the template T1w anatomical image and visually inspected to ensure that the circles encompassing the ROIs did not encompass adjacent structures. These ROIs were then transformed to each individual subject's imaging space using the diffeomorphic transform. These ROIs were chosen based on areas of known relatively high myelination (PLIC) and very low myelination (optic radiations) at term birth.

Validation of the Ratio Technique

All statistical analyses were performed in Matlab (MathWorks). T1w, T2w, ADC, and ratio images were averaged across subjects to create mean images for qualitative comparison. Because myelination is known to be associated with reduced diffusion, we tested whether this relationship was maintained despite the contrast reversal found in the neonatal brain by evaluating the correlation of ADC values with the ratio images in the PLIC and optic radiations using a linear regression analysis. For this regression analysis, we calculated the slope, intercept, P value, and coefficient of determination, R^2.

We also performed a quantitative comparison of perceived differences in contrast among the image types by calculating Michelson contrast, a measure of the difference between high and low luminance intensities in an image.[27] Michelson contrast provides a measurement that is reproducible and able to be compared across individuals. This measurement was used because the ratio images are intended to be viewed by humans for diagnostic assessment and assumes that the viewer is visually adapted to the sum of the background and foreground, a likely condition during clinical evaluation. The mean intensity values of the PLIC and optic radiation ROIs were computed and used to calculate the Michelson contrast:

$$MC = \frac{I_{max} - I_{min}}{I_{max} + I_{min}}$$

where I_{max} was assumed to be the mean intensity value of the PLIC ROI and I_{min} was assumed to be the mean intensity value of the optic radiation ROI[27] Comparisons of Michelson contrast between image types were made using a two-tailed unpaired Student's t-test ($P < 0.05$).

Lastly, slice-by-slice evaluation of the corticospinal tract was performed in MRIcro, an open source image viewer (http://www.cabiatl.com/mricro/mricro/), to provide subjective assessment of the ability of the T1w/T2w ratio to visualize myelinated structures in comparison to T1w and T2w images.[28] Extraction of the corticospinal tract was performed using ITK-SNAP's semi-automated active contour segmentation.[29] The image was manually thresholded to enhance the contrast of the PLIC, and a seed was placed on both posterior limbs and allowed to fill the volume of areas with similar imaging characteristics—in this case, the corticospinal tract. Surface rendering of the volume was subsequently done in Matlab. This was performed for the mean T1w, mean T2w, and mean ratio images (i.e., averaged across subjects in template space).

Results

T1w, T2w, and ratio images, averaged across all subjects, are shown in Figure 2, demonstrating qualitatively that the ratio image provides greater contrast of known myelinated areas (e.g., the corticospinal tract) compared with T1w and T2w images. Linear regression analysis of ratio versus ADC values showed a significant negative relationship between the two (Fig. 3; intercept = 1.26, slope = −0.0006, $R^2 = 0.96$, and $P < 0.001$), indicating that the relationship of myelination to restricted diffusion is preserved. Quantitative assessment

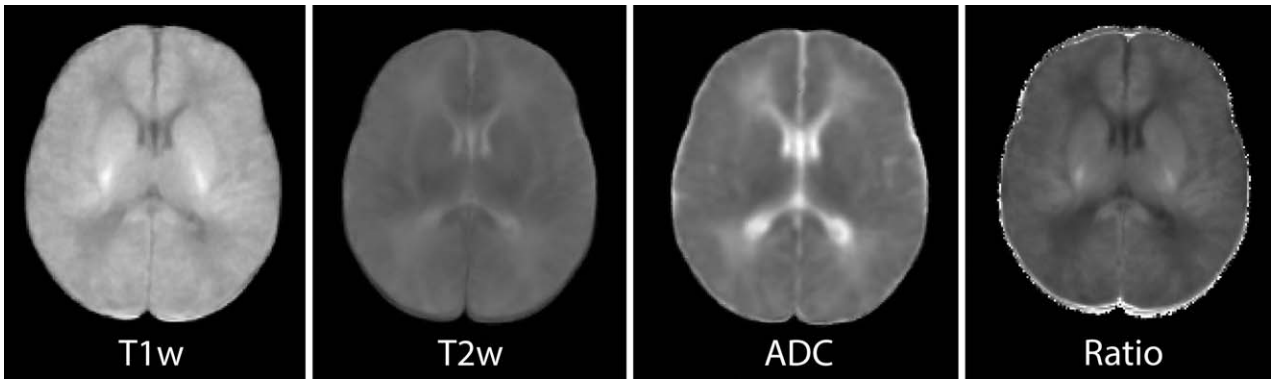

FIGURE 2: T1w, T2w, ADC, and ratio images (left to right) averaged across subjects. Axial slices are at the level of the posterior limbs of the internal capsules and optic radiations.

using Michelson contrast showed means and standard deviations of this measure of intrinsic contrast to be 0.17 ± 0.02, 0.11 ± 0.03, 0.15 ± 0.03, and 0.27 ± 0.04 for T1w, T2w, ADC, and ratio images, respectively. The Michelson contrast for the T1w/T2w ratio was 1.6 times higher than T1w, 2.6 times higher than T2w images, and 1.76 times higher than ADC images (all $P < 0.001$ using a two-tailed unpaired Student's t-test) (Fig. 4).

The corticospinal tract is subjectively much more easily visualized on the mean ratio image than the T1w and T2w images and can be traced through its entire intracranial course from the brainstem, through the posterior limbs of the internal capsule, and terminating with some fibers extending into the motor cortex (Fig. 5; see Supplementary Movie S2 of volume renderings of the ratio, T1w image (Supplementary Movie S3), and T2w image (Supplementary Movie S4).

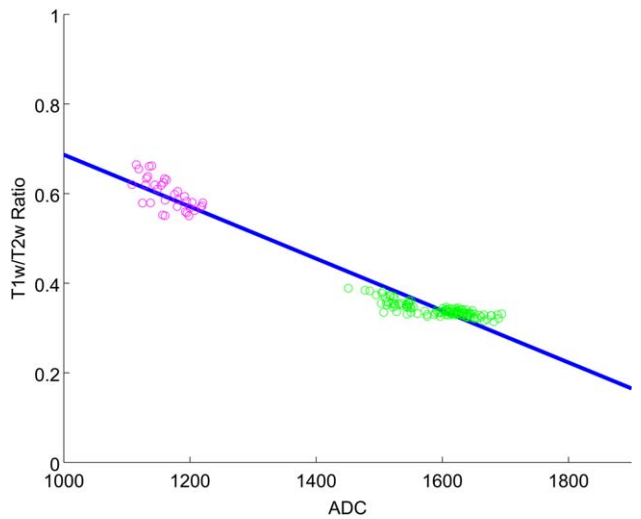

FIGURE 3: Regression of T1w/T2w ratio intensity values on the ADC values demonstrates a significant negative relationship ($R^2 = 0.96$; $P < 0.001$). Purple dots represent the PLIC voxels and green dots represent the OR voxels. ADC values are thresholded between 1000 and 1900 $\mu m^2/s$ to eliminate noise from extracranial structures.

Discussion

T1 relaxation time is thought to reflect the amount of cholesterol and galactocerebroside in the brain[16,30]; whereas, T2 relaxation time reflects various macromolecular processes of mature myelin, including decreased free water and increased hydrophobicity.[18,31,32] The ratio of the two image types takes advantage of the different properties of T1 and T2 relaxation to increase intrinsic contrast and better visualize myelin. Although used successfully in adults to increase myelin contrast,[11–14] the different tissue properties in the developing brain raise questions about its utility in neonates. However, if shown to be effective, the T1w/T2w ratio could improve the ability to diagnose myelin abnormalities in the developing brain. Furthermore, because this method uses routinely acquired clinical sequences, it does not add any additional scan time, an important consideration in the neonatal population where motion typically represents a major limiting factor in image quality.

Our results provide two sources of evidence suggesting that the T1w/T2w ratio is sensitive to myelin density in

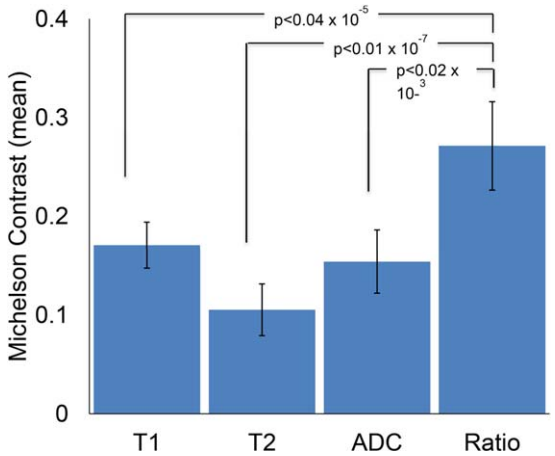

FIGURE 4: Comparison of mean Michelson contrast of T1w, T2w, ADC, and ratio images of all subjects. The Michelson contrast for ratio images is 1.6 times higher than T1w images, 2.6 times higher than T2w images, and 1.8 times higher than ADC images.

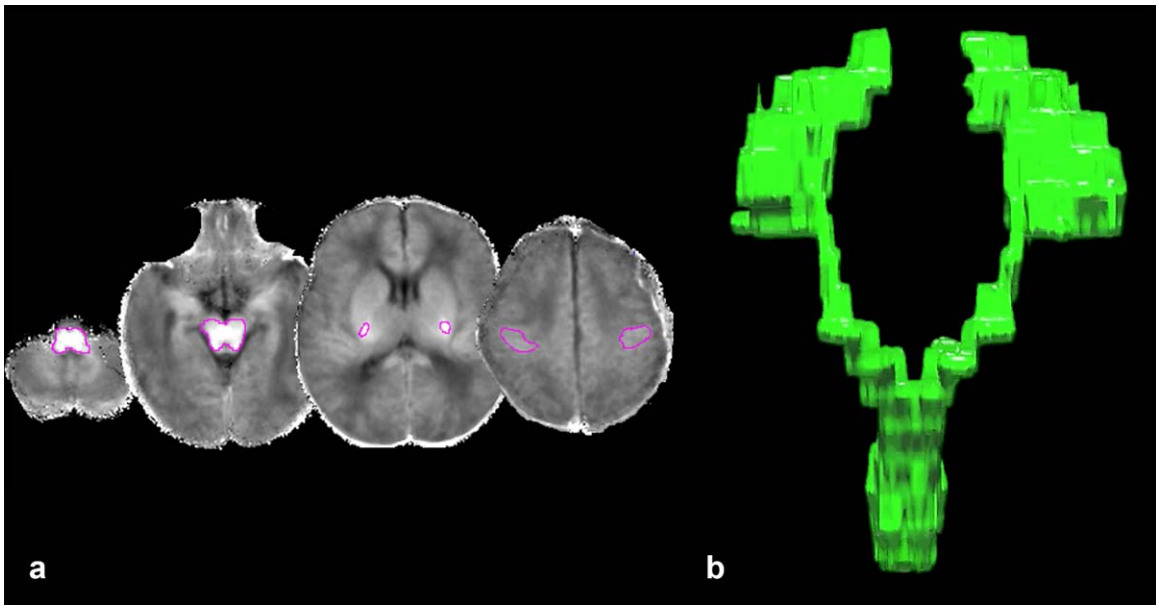

FIGURE 5: Panel A demonstrates a multi-slice representation of the corticospinal tract (outlined in violet) derived from the ratio technique shown on the mean ratio image. Axial slices are through the brain stem, posterior limbs of the internal capsule, and the motor cortex. Panel B is a still image of a volume rendering of the corticospinal tract from the ratio image. A rotating version of this volume rendering can be found in the Supplementary Movie S2.

neonates, as it is in adults. First, we found a significant negative association between areas of high ratio intensity values and corresponding areas of low ADC values. This corroborates prior studies demonstrating that ADC is lower in highly myelinated regions, perhaps reflecting decreased diffusivity as myelin forms.[5,33] Second, the T1w/T2w ratio showed high intensity values in the PLIC and low values in the optic radiations, which is consistent with the rapid brain maturation in the first few months of life that results in large spatial variations in myelin density. The rapid brain maturation in the first few months of life results in large spatial variations in myelin density. Our findings support previous studies that show the PLIC is largely myelinated by term birth, whereas, myelination of the optic radiation has not fully developed[10,16,18–21] These findings indicate that, despite differences in neonatal tissue properties in comparison to adults, the T1w/T2w ratio appears to be measuring myelin density.

Our results support previous work that has shown how a ratio method can be helpful in evaluating neonatal white matter.[15] We expanded on these findings by quantifying improvement of intrinsic contrast over T1w and T2w images alone. The ratio technique provided at least a 60% improvement in myelin contrast over routine clinical T1w, T2w, or ADC images in neonates. The greater contrast allowed us to trace the expected course of the corticospinal tract, which is not easily discernible on routine imaging.

Although the patients included in this study were reviewed as grossly normal, the clinical indications suggest that there may be underlying undetected abnormalities. If our assumption of normal brain morphology were false, any reductions in myelin due to undetected delays in myelin development would have minimal effects in regions that normally have low myelin, such as the optic radiations. It could, however, have a greater effect on regions of high myelination, such as the PLIC, but, such reductions in myelin would theoretically *reduce* intrinsic contrast differences between the posterior limb and optic radiations. Thus, the improvements in contrast we detected using the ratio technique should be viewed as a conservative estimate, especially in cases of undetected developmental delays, and would likely result in even larger effect sizes in a true "normal" group.

Another potential limitation is the possibility that some patients in the group may have suffered HII. Prior studies have shown that severe HII may lead to hyperintense T1w signal in areas such as the PLIC.[34] While no HII was reported for any patient in our cohort, undetected, subthreshold effects of hypoxia could elevate the T1w signal intensity in the PLIC and be misinterpreted as myelin. However, we believe it is highly unlikely that HII was both present and had effects that were located exclusively within the PLIC in all or even some of our patients.

To compare different sequences, co-registration was required. There were subtle misregistration artifacts of the T1w and T2w images, especially at the cerebrospinal–gray matter interfaces. This may provide false increases in contrast, which could be misinterpreted as myelin pathology. While we focused on central white matter areas of the brain in this study, future studies could examine whether these artifacts affect detection of intracortical myelin.

Although all studies were performed on the same MRI scanner, there were differences in technique, with 6 of the

10 using volumetric scans and 4 using 2D scans. Additional analyses of different sequence types (e.g., 2D and 3D) are ongoing to see if sequence type affects contrast improvement. Optimal pulse sequence parameters for the visualization of myelin in term neonates may vary with field strength,[35] and the value of the ratio technique at 3T remains to be determined.

Finally, it may be possible to fully automate the processing pipeline, which could open the door for real-time assessment at the radiologist's workstation. We plan to conduct future studies using larger patient cohorts to compare normal and delayed myelination in the various stages of development. In addition to HII, there are numerous developmental disorders, such as leukodystrophies, metabolic diseases, or in utero injuries that are characterized by delayed myelination or myelin reductions. By accentuating intrinsic contrast between areas with different degrees of myelination, the T1w/T2w ratio may improve detection of normal and abnormal myelination patterns in the neonatal brain.

References

1. Liauw L, van der Grond J, van den Berg-Huysmans AA, Palm-Meinders IH, van Buchem MA, van Wezel-Meijler G. Hypoxic-ischemic encephalopathy: diagnostic value of conventional MR imaging pulse sequences in term-born neonates. Radiology 2008;247:204–212.
2. Rutherford MA, Ward P, Malamateniou C. Advanced MR techniques in the term-born neonate with perinatal brain injury. Semin Fetal Neonat Med 2005;10:445–460.
3. Geng X, Gouttard S, Sharma A, et al. Quantitative tract-based white matter development from birth to age 2years. Neuroimage 2012;61:542–557.
4. Hermoye L, Saint-Martin C, Cosnard G, et al. Pediatric diffusion tensor imaging: normal database and observation of the white matter maturation in early childhood. Neuroimage 2006;29:493–504.
5. Provenzale JM, Isaacson J, Chen S, Stinnett S, Liu C. Correlation of apparent diffusion coefficient and fractional anisotropy values in the developing infant brain. AJR Am J Roentgenol 2010;195:W456–W462.
6. Toft PB, Leth H, Peitersen B, Lou HC, Thomsen C. The apparent diffusion coefficient of water in gray and white matter of the infant brain. J Comput Assist Tomogr 1996;20:1006–1011.
7. Gao J, Li X, Li Y, et al. Differentiating T2 hyperintensity in neonatal white matter by two-compartment model of diffusional kurtosis imaging. Sci Rep 2016;6:24473.
8. Engelbrecht V, Rassek M, Preiss S, Wald C, Modder U. Age-dependent changes in magnetization transfer contrast of white matter in the pediatric brain. AJNR Am J Roentgenol 1998;19:1923–1929.
9. Deoni SC, Mercure E, Blasi A, et al. Mapping infant brain myelination with magnetic resonance imaging. J Neurosci 2011;31:784–791.
10. Dubois J, Dehaene-Lambertz G, Kulikova S, Poupon C, Huppi PS, Hertz-Pannier L. The early development of brain white matter: a review of imaging studies in fetuses, newborns and infants. Neuroscience 2014;276:48–71.
11. Glasser MF, Van Essen DC. Mapping human cortical areas in vivo based on myelin content as revealed by T1- and T2-weighted MRI. J Neurosci 2011;31:11597–11616.
12. Ganzetti M, Wenderoth N, Mantini D. Whole brain myelin mapping using T1- and T2-weighted MR imaging data. Front Hum Neurosci 2014;8:671.
13. Grydeland H, Walhovd KB, Tamnes CK, Westlye LT, Fjell AM. Intracortical myelin links with performance variability across the human lifespan: results from T1- and T2-weighted MRI myelin mapping and diffusion tensor imaging. J Neurosci 2013;33:18618–18630.
14. Shafee R, Buckner RL, Fischl B. Gray matter myelination of 1555 human brains using partial volume corrected MRI images. Neuroimage 2015;105:473–485.
15. Lee K, Cherel M, Budin F, et al. Early postnatal myelin content estimate of white matter via T1w/T2w Ratio. Proceedings of SPIE--the International Society for Optical Engineering 2015;9417.
16. Barkovich AJ. Concepts of myelin and myelination in neuroradiology. AJNR Am J Neuroradiol 2000;21:1099–1109.
17. Liauw L, Palm-Meinders IH, van der Grond J, et al. Differentiating normal myelination from hypoxic-ischemic encephalopathy on T1-weighted MR images: a new approach. AJNR Am J Neuroradiol 2007;28:660–665.
18. Dietrich RB, Bradley WG, Zaragoza EJt, et al. MR evaluation of early myelination patterns in normal and developmentally delayed infants. AJNR Am J Neuroradiol 1988;150:889–896.
19. Paus T, Collins DL, Evans AC, Leonard G, Pike B, Zijdenbos A. Maturation of white matter in the human brain: a review of magnetic resonance studies. Brain Res Bull 2001;54:255–266.
20. Brody BA, Kinney HC, Kloman AS, Gilles FH. Sequence of central nervous system myelination in human infancy. I. An autopsy study of myelination. J Neuropathol Exp Neurol 1987;46:283–301.
21. Kinney HC, Brody BA, Kloman AS, Gilles FH. Sequence of central nervous system myelination in human infancy. II. Patterns of myelination in autopsied infants. J Neuropathol Exp Neurol 1988;47:217–234.
22. Jenkinson M, Bannister P, Brady M, Smith S. Improved optimization for the robust and accurate linear registration and motion correction of brain images. Neuroimage 2002;17:825–841.
23. Jenkinson M, Beckmann CF, Behrens TEJ, Woolrich MW, Smith SM. FSL. Neuroimage 2012;62:782–790.
24. Smith SM. Fast robust automated brain extraction. Hum Brain Mapp 2002;17:143–155.
25. Zhang Y, Brady M, Smith S. Segmentation of brain MR images through a hidden Markov random field model and the expectation-maximization algorithm. IEEE Trans Med Imaging 2001;20:45–57.
26. Avants BB, Tustison NJ, Song G, Cook PA, Klein A, Gee JC. A reproducible evaluation of ANTs similarity metric performance in brain image registration. Neuroimage 2011;54:2033–2044.
27. Michelson AA. Studies in optics. Chicago, IL: University of Chicago Press; 1927.
28. Rorden C, Brett M. Stereotaxic display of brain lesions. Behav Neurol 2000;12:191–200.
29. Yushkevich PA, Piven J, Hazlett HC, et al. User-guided 3D active contour segmentation of anatomical structures: significantly improved efficiency and reliability. Neuroimage 2006;31:1116–1128.
30. Koenig SH, Brown RD III, Spiller M, Lundbom N. Relaxometry of brain: why white matter appears bright in MRI. Magn Reson Med 1990;14:482–495.
31. Barkovich AJ, Kjos BO, Jackson DE Jr, Norman D. Normal maturation of the neonatal and infant brain: MR imaging at 1.5 T. Radiology 1988;166(Pt 1):173–180.
32. Svennerholm L, Vanier MT. Lipid and fatty acid composition of human cerebral myelin during development. Adv Exp Med Biol 1978;100:27–41.
33. Engelbrecht V, Scherer A, Rassek M, Witsack HJ, Modder U. Diffusion-weighted MR imaging in the brain in children: findings in the normal brain and in the brain with white matter diseases. Radiology 2002;222:410–418.
34. Rutherford MA, Pennock JM, Counsell SJ, et al. Abnormal magnetic resonance signal in the internal capsule predicts poor neurodevelopmental outcome in infants with hypoxic-ischemic encephalopathy. Pediatrics 1998;102(Pt 1):323–328.
35. Tyan AE, McKinney AM, Hanson TJ, Truwit CL. Comparison of spin-echo and gradient-echo T1-weighted and spin-echo T2-weighted images at 3T in evaluating term-neonatal myelination. AJNR Am J Neuroradiol 2015;36:411–416.