Published in final edited form as:

Pediatr Neurol. 2013 December ; 49(6): 424–430. doi:10.1016/j.pediatrneurol.2013.08.026.

Automatically Quantified Diffuse Excessive High Signal Intensity on MRI Predicts Cognitive Development in Preterm Infants

Nehal A. Parikh, DO, MS^{1,2,3}, Lili He, PhD¹, Eliana Bonfante-Mejia, MD⁴, Leo Hochhauser, MD⁴, Patricia Evans Wilder, MD³, Katrina Burson, RN³, and Supreet Kaur, MS¹

¹Center for Perinatal Research, The Research Institute at Nationwide Children's Hospital, Columbus, OH, United States

²The Department of Pediatrics, Ohio State University College of Medicine, Columbus, OH, United States

³Department of Pediatrics, Division of Neonatology, University of Texas Health Science Center, Houston, TX

⁴Department of Radiology, University of Texas Health Science Center, Houston, TX

Abstract

Background—Cognitive and language impairments constitute the majority of disabilities observed in preterm infants. It remains unclear if diffuse excessive high signal intensity (DEHSI) on MRI at term represents delayed white matter maturation or pathology.

Methods—We hypothesized that diffusion tensor imaging-based objectively quantified DEHSI measures at term will be strong predictors of cognitive and language development at 2 years in a cohort of 41 extremely low birth weight (ELBW; <1000g) infants. Using an automated probabilistic atlas, mean diffusivity maps were used to objectively segment and quantify DEHSI volume and mean, axial, and radial diffusivity measures. Standardized neurodevelopment was assessed at 2 years of age using the Bayley Scales of Infant Development, third edition.

Results—Thirty-six of the 41 infants (88%) had complete developmental data at follow-up. Objectively quantified DEHSI volume correlated significantly with cognitive and language scores at 2 years ($P < 0.001$ for both). The sum values of the three diffusivity measures in detected DEHSI regions also correlated significantly with the Bayley scores (R^2 34.7%; $P < 0.001$ for each). Infants in the highest quartile for DEHSI volumes had scores between 19–24 points lower than infants in the lowest quartile ($P < 0.01$). When diagnosed subjectively by neuroradiologists however, Bayley scores were not significantly lower in infants with extensive DEHSI.

Conclusions—These findings lend further evidence that DEHSI is pathologic and that objectively quantified diffusion-based DEHSI volume at term is associated with cognitive and language impairments. Our approach could be utilized for risk stratification and early intervention for such high-risk extremely preterm infants.

© 2013 Elsevier Inc. All rights reserved.

Corresponding author: Nehal A. Parikh, DO, MS, Center for Perinatal Research, Nationwide Children's Hospital, 575 Children's Crossroad, Columbus, OH 43215, USA, 614.355.6657 Voice, 614.355.5899 Fax, Nehal.Parikh@nationwidechildrens.org.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Keywords

diffuse excessive high signal intensity; magnetic resonance imaging; diffusion tensor imaging; extremely low birth weight infant; infant; preterm; neurodevelopment; Bayley exam; outcome; prognosis

Introduction

While survival rates have improved dramatically for extremely preterm infants in the past two decades, the incidence and prevalence of neurodevelopmental impairments are increasing.^{1,2} Cognitive and language impairments constitute the majority of impairments observed in extremely low birth weight (ELBW) and very preterm (<30 weeks gestational age) infants.^{3,4} The precise neuroimaging correlates of such impairments remains elusive. Recent neuropathologic studies indicate the high incidence of diffuse non-cystic periventricular leukomalacia in very preterm infants as a possible antecedent to such impairments.⁵ Earlier evidence suggested the presence of white matter hyperintensities on T2-weighted MRI, called diffuse excessive high signal intensity (DEHSI), to be a significant predictor of lower developmental quotient at 18 to 36 months corrected age.^{6,7} Subsequent studies have been unable to replicate this correlation, except in infants with severe DEHSI that were defined as exhibiting intense signal abnormality resulting in an absence of posterior periventricular crossroads.^{8–12} However, the definition of DEHSI across studies was inconsistent and diagnosis was subjectively made using qualitative MRI, possibly contributing to these conflicting findings.

There is an urgent need to translate our current understanding of the pathogenesis of perinatal brain injury and aberrant brain development into improved diagnosis, prognosis, and prevention measures. Advances in MRI acquisition and post-processing techniques are ripe for translation to enhance injury diagnosis and outcome prediction in this high-risk population. For example, when investigators quantitated microstructural properties using diffusion tensor imaging (DTI) in the centrum semiovale, a white matter region that is commonly affected by DEHSI, they observed a significant correlation with cognitive development.^{7,8,13} However, the extent of DEHSI (e.g. volume) was not quantified and study regions were chosen irrespective of DEHSI boundaries, possibly diluting relationship with outcomes. We hypothesized that the combined use of DTI-defined DEHSI volume and diffusion measures, when objectively measured and quantified will be strong predictors of cognitive and language development at 18 to 22 months corrected age in a cohort of ELBW infants. We further hypothesized that such objectively quantified DEHSI measures will be stronger predictors of development than subjectively diagnosed DEHSI by neuroradiologists.

Materials and Methods

Subjects

The study population was derived from an imaging cohort of 50 ELBW (birth weight 1000g) infants without any major congenital anomalies affecting the brain from the Children's Memorial Hermann Hospital NICU. Nine infants were excluded – five due to severe injury (hemorrhage and encephalomalacia), three with image artifacts and one infant that died after discharge with a history of severe parenchymal hemorrhage – leaving a study population of 41 ELBW infants. Dates of enrollment were May 2007 to July 2009. Institutional review board approved the study and written parental informed consent was obtained for every subject.

MRI acquisition

MRI scans at 3 T (Philips scanner) were obtained with use of an eight-channel SENSE-compatible phased array receive head coil. For each subject, prior to DTI, we performed a dual-echo fast-spin-echo sequence to obtain proton-density- and T2-weighted scans. The imaging parameters used were: TE1 = 8.75ms; TE2 = 175 ms; TR = 10,000 ms; flip angle = 90°; FOV = 180×180 mm²; the imaging matrix = 256×256 mm²; slice thickness = 2 mm. Single shot EPI DTI was acquired in 15 non-collinear directions using the parameters: TR = 6000 ms; TE = 61 ms; FOV = 180×180 mm²; the imaging matrix = 128×128 mm²; slice thickness = 2 mm; high b-value = 800 s/mm²; low b-value = 0; SENSE factor = 2. An experienced neonatal transport nurse and research nurse transported all infants to the MRI scanner after feeding, swaddling and placement of silicone ear plugs (E.A.R. Inc., Boulder, CO) and Natus MiniMuffs (Natus Medical Inc., San Carlos, CA). All scans were completed under the supervision of a neonatal research nurse and a neonatologist experienced in neonatal MRI without the use of any sedation. One of two neuroradiologists read all anatomic MRI using a standardized reporting form.

Diffusion parameter maps

Images were skull-stripped using Brain Extraction Tool.¹⁴ Any eddy current and motion artifacts were corrected using FSL (FMRIB Oxford, UK) software's diffusion toolbox.¹⁵ Diffusion weighted images were affine aligned to the mean diffusion weighted image across all directions. Diffusion tensors and parameter maps of apparent diffusion coefficient (ADC)/mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD) were generated using DTI Studio (Johns Hopkins).¹⁶

We focused on automatically segmenting DEHSI only in the centrum semiovale region (two axial slices immediately above the lateral ventricles). This permitted selecting the region of white matter that is most affected by DEHSI and reduce measurement errors due to normal crossing fibers in frontal and occipital periventricular white matter regions which also result in high signal intensities and obscure DEHSI boundaries.^{17,18} Cerebral tissues (white matter and gray matter) were segmented from T2-weighted structural images. This was achieved by incorporating the segmentation from SPM8 software (Wellcome Department of Imaging Neuroscience, [University College London](#)) with anatomical information obtained from an infant probabilistic brain atlas. The atlas was built from a set of 19 manual parcellations of ELBW brains randomly selected from our cohort. The atlas creation followed the general procedure of creating a group-averaged atlas.¹⁹ The generated cerebral tissue binary masks were superimposed on MD maps. Next, voxels with MD values greater than or equal to 1.4 standard deviation (SD) above the mean of tissues were defined as DEHSI, following the same strategy as described in He and Parikh.²⁰ The detected binary DEHSI masks were then superimposed on the parameter maps to calculate the regional average, variance, and sum/total values of MD, AD and RD measures in detected DEHSI regions. Total values of MD (referred to as MD sum) was derived by summing the MD values from all voxels identified as DEHSI from the MD maps. Sum values for AD and RD were derived using a similar approach. The total DEHSI segmented lesion volume was calculated as the total number of voxels containing the segmented area, multiplied by the planar dimensions of the voxels and the thickness of the brain slice. All volumes are presented as mm³ (equivalent to mL).

Language and cognitive developmental outcomes

All discharged ELBW infants were invited back at 18 to 22 months corrected age and administered a standardized Bayley Scales of Infant and Toddler Development III (BSID-III). The BSID-III cognitive and language subtests (on a scale of 50 to 150, with a mean of

100 and 150 indicating the most advanced development) were administered by a masked, certified examiner. All examiners are blinded to imaging findings during assessment.

Statistical Analyses

We defined low BSID-III scores as cognitive or language scores less than 90. This equates to approximately 1 SD below the mean of healthy term controls.²¹ We used One-Way ANOVA analysis to determine any significant difference between mean DEHSI measures in subjects with normal BSID-III evaluation scores (≥ 90) and those with low scores (<90). Next, Pearson correlation and simple linear regression analyses were employed to assess objectively quantified DEHSI measures (volumes, MD, AD and RD sum values) within detected DEHSI regions and BSID-III testing scores (language and cognitive). In bivariate linear regression analyses, we tested the individual effects of gestational age, sex, maternal education, white matter injury on cranial ultrasound, abnormal structural MRI, and postmenstrual age at MRI, on the relationship of DEHSI volume with BSID-III scores. Two neuroradiologists qualitatively defined DEHSI by using a standardized definition of DEHSI. Infants with less than one-third involvement of white matter were defined as mild, two-thirds as moderate, and those with involvement throughout the white matter were diagnosed with severe DEHSI. Cohen's kappa statistic was used to assess intra-rater reliability for repeated reading, separated by several months, of 25 randomly selected cases by one of the study neuroradiologists (EBM).²²

Objectively detected DEHSI volume was categorized into three groups: no or mild DEHSI if volume was in lowest quartile ($<25\%$), moderate when volume was 25th to 74th%, and severe DEHSI if volume was in the highest quartile ($\geq 75\%$) for the group. One-Way ANOVA analysis was conducted to determine any significant group differences in BSID-III scores based on subjectively and objectively defined DEHSI severity. Two-sided P values of less than .05 were considered to indicate statistical significance. All analyses were performed using Microsoft Excel (2010 version) and Stata 11.0 (StataCorp, College Station, Texas).

Results

Thirty-nine of the 41 eligible infants (95%) returned for follow-up at a mean (SD) age of 23.7 (3.0) months of age (20.0 months corrected age). Three of these infants exhibited behavioral problems and could not be tested for both BSID-III scores. Therefore, 36 ELBW infants were available for full analyses. Table 1 lists the baseline characteristics of our 36 ELBW infants with full outcomes data. Owing to the extremely low birth weight inclusion criteria, study infants incurred frequent neonatal morbidities. Figure 1 displays three separate MRI scans at the level of the centrum semiovale with mild, moderate, and severe degrees of DEHSI that were objectively segmented using MD maps. The mean (SD) DEHSI volume for the group in the centrum semiovale was 792.6 (225.1) mm³ (range: 344.1 – 1238.0 mm³).

The mean (SD) BSID-III cognitive and language scores at 2 years were 96 (12) and 90 (16), respectively. Objectively measured DEHSI volume when assessed as continuous outcomes correlated significantly with BSID-III language and cognitive scores at 2 years of age ($P<0.001$ for both). The sum values of the three diffusivity measures within detected DEHSI regions – mean, axial, and radial – also correlated significantly with the BSID-III scores (Table 2; Figure 2). However, MD, AD, and RD average or variance values did not. Of our 10 DEHSI based measurements, MD sum and AD sum values showed the strongest correlation with BSID-III scores – R^2 of 34.7% (Table 2; Figure 2). In bivariate linear regression analyses, gestational age, sex, maternal education, white matter injury on cranial ultrasound, abnormal structural MRI, and postmenstrual age at MRI scan had minimal effect

on the coefficients (<10% change) and no effect on the significant relationships between DEHSI volumes and BSID-III scores.

Eight ELBW infants (22%) had low BSID-III scores (<90) and 17 (47%) had low language scores (<90). Study infants with abnormal cognitive and language scores exhibited significantly higher DEHSI volume as well as MD sum, AD sum, and RD sum in detected DEHSI regions (Table 3). Based on standardized qualitative neuroradiologist readings on conventional T2-weighted MRI at term, 19 infants had mild DEHSI, 16 infants had moderate, and one infant was diagnosed with severe DEHSI. The intra-rater reliability for DEHSI diagnosis was moderate, with a kappa measure of 0.34 (95% CI: 0.06, 0.77). Bayley scores were not significantly different in infants with varying degrees of DEHSI when subjectively diagnosed by neuroradiologists (Table 4). When infants with moderate and severe DEHSI were combined and compared to infants with no/mild DEHSI, the results remained statistically insignificant ($P>0.60$ for both scores). However, when DEHSI volumes were objectively quantitated, cognitive and language scores differed significantly between groups (Table 4). Infants in the highest quartile for DEHSI volumes (severe) had scores between 19 to 24 points lower than infants in the lowest quartile (mild) ($P<0.01$).

Discussion

This study shows that DTI-based objectively quantified measures such as MD sum and total lesion volume in detected DEHSI regions are early and significant predictor of developmental cognitive and language scores. Subjectively diagnosed neuroradiologist readings on the other hand are not. This is the first study to correlate DEHSI lesion volume with developmental scores. The accuracy that we observed in predicting cognitive development resulted in large part due to our ability to automatically segment DEHSI and quantify lesion volume using trace diffusivity maps. Unlike prior studies however, diffusivity measures alone did not correlate with developmental scores. Rather, extent of DEHSI, as measured by 3-dimensional volume rather than microstructural diffusivity, appears to be a stronger predictor of BSID-III scores.

Objective qualitative diagnosis of DEHSI is difficult and often lacks in sufficient reliability.²³ Signal inhomogeneity is commonly present on conventional MRI and image quality is highly dependent on institutional quality control measures. Furthermore, the normal presence of developmental crossroads – an area of multiple crossing fibers and rich extracellular matrix – in frontal and occipital periventricular white matter can also confound DEHSI diagnosis.^{8,17,18} The resulting measurement error has likely contributed to the conflicting associations with cognitive outcomes, reported to date. All prior studies that did not observe an association between DEHSI diagnosis at term and later developmental scores employed a qualitatively defined diagnosis of DEHSI and/or subjectively placed regions of interest,^{9–12} whereas three out of the five studies that observed a significant association used quantitative diffusion measures within typical regions of DEHSI.^{6–8,13,24}

Such variability in DEHSI definition, lesion sampling, and associated neurodevelopmental outcomes has fueled the debate about the nature of DEHSI and whether it represents a developmental delay in white matter maturation or a pathologic lesion, akin to subtle noncystic periventricular leukomalacia.^{5,7–9,25} Lack of any imaging-neuropathologic correlation studies, in part because majority of such infants survive, has introduced further doubt about the pathological significance of DEHSI. However, several inflammation-initiating illnesses, including sepsis, necrotizing enterocolitis, and bronchopulmonary dysplasia/prolonged mechanical ventilation, that have been linked with cognitive impairments²⁶ have also been associated with DEHSI.^{13,27–29} Furthermore, most investigators,^{8,25,30,31} but not all⁹ have observed significant differences in diffusion

measures between infants with and without DEHSI and similarity in diffusion between infants with DEHSI and cystic periventricular leukomalacia.³² These findings suggest that DEHSI is pathologic. Our findings using more objective measurements of DEHSI, lend further evidence that DEHSI on conventional T2-weighted MRI at term in preterm infants is pathologic and is associated with abnormal cognitive and language development at 2 years of age.

We employed DTI-based contrast to automatically segment and quantify the extent/volume of DEHSI in the centrum semiovale. While white matter microstructural development has been quantified in preterm infants using manually placed regions of interest in known or suspected regions of DEHSI,^{8,25,30,31} the same diffusion properties had not been exploited to objectively segment DEHSI regions and quantify its extent. We previously reported the use of T2-weighted contrast²⁷ and T2 relaxation properties²⁰ to automatically segment DEHSI volume; while these have their advantages, DTI-based segmentation likely reflects white matter microstructural development and pathology more closely. Further, this approach facilitates the use of objective region of interest-based microstructural measurements. Additional study strengths included the use of a high-field strength 3 Tesla magnet MRI scanner equipped with 32-channel coil. Using the latest (third) edition of the Bayley Scales, we were also able to define the significant relationship of DEHSI with language development. Iwata et al.²⁴ also observed a correlation between DEHSI and verbal intelligence quotient and found this relationship persisted until 9 years of age in very low birth weight infants.

Our study had certain limitations. While we were also able to follow all but two subjects to 2 years of age, three additional subjects could not be fully tested due to behavioral issues. Improvements in our segmentation methods to accurately detect and include periventricular white matter DEHSI may enhance prediction of cognitive and language development. Additionally, our relatively small sample size may have exhibited limited power for some of the outcomes examined, such as with mean MD, AD, and RD based prediction of BSID-III scores. A larger study to validate our findings is therefore important. Furthermore, longer follow-up to 6-years is also essential as early diagnosis of cognitive impairment at 2 years is only moderately correlated with intellectual impairments at school age.³³

The degree of cognitive impairment that we observed in infants with moderate to severe DEHSI, compared to those with no/mild DEHSI, was comparable to the five prior studies that reported significant differences.^{6-8,13,24} Preterm infants from the Imperial College, UK-based studies exhibited up to 20-point differences in developmental quotient between groups,^{6,7,13} while those from Australia and Japan exhibited smaller,^{8,24} yet still clinically meaningful 11-point decreases in Bayley mental scores and intelligence scores, respectively. As cognitive impairments are the most common neurodevelopmental abnormality in preterm infants,⁴ early prediction at term is crucial for early detection and targeted selection of early intervention therapies.^{34,35} Yet, current neuroimaging studies lack sufficient sensitivity to detect the highest risk infants.^{24,36,37} Infants with objectively diagnosed moderate to severe DEHSI likely represent a readily identifiable subset of extremely preterm infants at very high risk for cognitive/intellectual impairments.

Conclusions

Objectively quantified DTI-defined DEHSI at term can facilitate early identification of infants at high risk for cognitive and language impairments. These findings lend further evidence that DEHSI is pathologic and associated with abnormal neurodevelopment at 2 years of age in ELBW infants. A larger study with school-age neurocognitive follow-up is important to validate our findings.

Acknowledgments

This work was supported by the National Center for Research Resources/Eunice Kennedy Shriver National Institute of Child Health and Human Development grant UL1 RR024148-04S3 (Best Pharmaceuticals for Children Act) and The Research Institute at Nationwide Children's Hospital (to NAP). The funding agencies played no role in the design, conduct, or analysis of the trial. The authors take full responsibility for the integrity of the data and analyses. We sincerely thank Vipulkumar S. Patel for his assistance with MRI data acquisition and the families and nurses that made this study possible.

References

1. Hintz SR, Kendrick DE, Vohr BR, et al. Changes in neurodevelopmental outcomes at 18 to 22 months' corrected age among infants of less than 25 weeks' gestational age born in 1993–1999. *Pediatrics*. 2005; 115(6):1645–1651. [PubMed: 15930228]
2. Wilson-Costello D, Friedman H, Minich N, Fanaroff AA, Hack M. Improved survival rates with increased neurodevelopmental disability for extremely low birth weight infants in the 1990s. *Pediatrics*. 2005; 115(4):997–1003. [PubMed: 15805376]
3. Tyson JE, Parikh NA, Langer J, et al. Intensive care for extreme prematurity--moving beyond gestational age. *New Engl J Med*. 2008; 358(16):1672–1681. [PubMed: 18420500]
4. Potharst ES, van Wassenae AG, Houtzager BA, van Hus JWP, Last BF, Kok JH. High Incidence of Multi-Domain Disabilities in Very Preterm Children at Five Years of Age. *J Pediatr*. 2011; 159(1): 79–85. [PubMed: 21349538]
5. Volpe JJ. Brain injury in premature infants: a complex amalgam of destructive and developmental disturbances. *Lancet Neurol*. 2009; 8(1):110–124. [PubMed: 19081519]
6. Dyet LE, Kennea N, Counsell SJ, et al. Natural history of brain lesions in extremely preterm infants studied with serial magnetic resonance imaging from birth and neurodevelopmental assessment. *Pediatrics*. 2006; 118(2):536–548. [PubMed: 16882805]
7. Boardman JP, Craven C, Valappil S, et al. A common neonatal image phenotype predicts adverse neurodevelopmental outcome in children born preterm. *Neuroimage*. 2010; 52(2):409–414. [PubMed: 20451627]
8. Kidokoro H, Anderson PJ, Doyle LW, Neil JJ, Inder TE. High Signal Intensity on T2-Weighted MR Imaging at Term-Equivalent Age in Preterm Infants Does Not Predict 2-Year Neurodevelopmental Outcomes. *AJNR Am J Neuroradiol*. 2011; 32(11):2005–2010. [PubMed: 21960493]
9. Hart A, Whitby E, Wilkinson S, Alladi S, Paley M, Smith M. Neuro-developmental outcome at 18 months in premature infants with diffuse excessive high signal intensity on MR imaging of the brain. *Pediatr Radiol*. 2011; 41(10):1284–1292. [PubMed: 21681616]
10. Jeon TY, Kim JH, Yoo SY, et al. Neurodevelopmental Outcomes in Preterm Infants: Comparison of Infants with and without Diffuse Excessive High Signal Intensity on MR Images at Near-term-equivalent Age. *Radiology*. 2012; 263(2):518–526. [PubMed: 22403166]
11. de Bruine FT, van den Berg-Huysmans AA, Leijser LM, et al. Clinical Implications of MR Imaging Findings in the White Matter in Very Preterm Infants: A 2-year Follow-up Study. *Radiology*. 2011; 261(3):899–906. [PubMed: 22031710]
12. Skjold B, Vollmer B, Bohm B, et al. Neonatal Magnetic Resonance Imaging and Outcome at Age 30 Months in Extremely Preterm Infants. *J Pediatr*. 2012; 160(4):559–566. [PubMed: 22056283]
13. Krishan ML, Dyet LE, Boardman JP, et al. Relationship between white matter apparent diffusion coefficients in preterm infants at term-equivalent age and developmental outcome at 2 years. *Pediatrics*. 2007; 120(3):e604–9. [PubMed: 17698966]
14. Smith SM. Fast robust automated brain extraction. *Hum Brain Mapp*. 2002; 17(3):143–155. [PubMed: 12391568]
15. Jenkinson M, Beckmann CF, Behrens TE, Woolrich MW, Smith SM. Fsl. *Neuroimage*. 2012; 62(2):782–790. [PubMed: 21979382]
16. Jiang H, van Zijl PC, Kim J, Pearlson GD, Mori S. DtiStudio: resource program for diffusion tensor computation and fiber bundle tracking. *Comput Methods Programs Biomed*. 2006; 81(2): 106–116. [PubMed: 16413083]

17. Judas M, Rados M, Jovanov-Milosevic N, Hrabac P, Stern-Padovan R, Kostovic I. Structural, immunocytochemical, and mr imaging properties of periventricular crossroads of growing cortical pathways in preterm infants. *AJNR Am J Neuroradiol*. 2005; 26(10):2671–2684. [PubMed: 16286422]
18. Kostovic I, Judas M, Rados M, Hrabac P. Laminar organization of the human fetal cerebrum revealed by histochemical markers and magnetic resonance imaging. *Cereb cortex*. 2002; 12(5): 536–544. [PubMed: 11950771]
19. Oishi K, Mori S, Donohue PK, et al. Multi-contrast human neonatal brain atlas: application to normal neonate development analysis. *Neuroimage*. 2011; 56(1):8–20. [PubMed: 21276861]
20. He L, Parikh NA. Automated detection of white matter signal abnormality using T2 relaxometry: application to brain segmentation on term MRI in very preterm infants. *Neuroimage*. 2013; 64:328–340. [PubMed: 22974556]
21. Moore T, Johnson S, Haider S, Hennessy E, Marlow N. Relationship between test scores using the second and third editions of the Bayley Scales in extremely preterm children. *J Pediatr*. 2012; 160(4):553–558. [PubMed: 22048046]
22. Landis JR, Koch GG. An application of hierarchical kappa-type statistics in the assessment of majority agreement among multiple observers. *Biometrics*. 1977; 33(2):363–374. [PubMed: 884196]
23. Hart AR, Smith MF, Rigby AS, Wallis LI, Whitby EH. Appearances of diffuse excessive high signal intensity (DEHSI) on MR imaging following preterm birth. *Pediatr Radiol*. 2010; 40(8): 1390–1396. [PubMed: 20333509]
24. Iwata S, Nakamura T, Hizume E, et al. Qualitative brain MRI at term and cognitive outcomes at 9 years after very preterm birth. *Pediatrics*. 2012; 129(5):e1138–1147. [PubMed: 22529280]
25. Counsell SJ, Shen Y, Boardman JP, et al. Axial and radial diffusivity in preterm infants who have diffuse white matter changes on magnetic resonance imaging at term-equivalent age. *Pediatrics*. 2006; 117(2):376–386. [PubMed: 16452356]
26. O'Shea TM, Shah B, Allred EN, et al. Inflammation-initiating illnesses, inflammation-related proteins, and cognitive impairment in extremely preterm infants. *Brain Behav Immun*. 2013; 29:104–112. [PubMed: 23295265]
27. Yu X, Zhang Y, Lasky RE, Datta S, Parikh NA, Narayana PA. Comprehensive brain MRI segmentation in high risk preterm newborns. *PloS one*. 2010; 5(11):e13874. [PubMed: 21079730]
28. Ball G, Counsell SJ, Anjari M, et al. An optimised tract-based spatial statistics protocol for neonates: applications to prematurity and chronic lung disease. *Neuroimage*. 2010; 53(1):94–102. [PubMed: 20510375]
29. Pogribna U, Yu X, Burson K, et al. Perinatal clinical antecedents of white matter microstructural abnormalities on diffusion tensor imaging in extremely preterm infants. *PLoS One*. 2013 In Press.
30. Cheong JY, Thompson DK, Wang HX, et al. Abnormal white matter signal on MR imaging is related to abnormal tissue microstructure. *AJNR Am J Neuroradiol*. 2009; 30(3):623–628. [PubMed: 19131414]
31. Skjold B, Horsch S, Hallberg B, et al. White matter changes in extremely preterm infants, a population-based diffusion tensor imaging study. *Acta Paediatr*. 2010; 99(6):842–849. [PubMed: 20132144]
32. Counsell SJ, Allsop JM, Harrison MC, et al. Diffusion-weighted imaging of the brain in preterm infants with focal and diffuse white matter abnormality. *Pediatrics*. 2003; 112(1):1–7. [PubMed: 12837859]
33. Hack M, Taylor HG, Drotar D, et al. Poor predictive validity of the Bayley Scales of Infant Development for cognitive function of extremely low birth weight children at school age. *Pediatrics*. 2005; 116(2):333–341. [PubMed: 16061586]
34. Vanderveen JA, Bassler D, Robertson CM, Kirpalani H. Early interventions involving parents to improve neurodevelopmental outcomes of premature infants: a meta-analysis. *J Perinatol*. 2009; 29(5):343–351. [PubMed: 19148113]
35. Nordhov SM, Ronning JA, Dahl LB, Ulvund SE, Tunby J, Kaarsen PI. Early intervention improves cognitive outcomes for preterm infants: randomized controlled trial. *Pediatrics*. 2010; 126(5):e1088–1094. [PubMed: 20937650]

36. Whitaker AH, Feldman JF, Van Rossem R, et al. Neonatal cranial ultrasound abnormalities in low birth weight infants: relation to cognitive outcomes at six years of age. *Pediatrics*. 1996; 98(1): 719–729. [PubMed: 8885952]
37. Woodward LJ, Anderson PJ, Austin NC, Howard K, Inder TE. Neonatal MRI to predict neurodevelopmental outcomes in preterm infants. *N Engl J Med*. 2006; 355(7):685–694. [PubMed: 16914704]

Figure 1. Representative Examples of Varying Degrees of DEHSI Detected Using Our Automated Segmentation Method

Raw axial T2-weighted images (left column) and MD maps in the centrum semiovale with segmented DEHSI highlighted in blue (right column), display representative examples of mild (top panel), moderate (middle), and severe DEHSI (lower panel).

Figure 2. Linear Regression Plots Demonstrate Relationship Between DESHI Measures and Developmental Scores

Regression plots display linear relationships between DESHI measures, volume (top panel), MD sum (second panel), AD sum (third panel), and RD sum (lowest panel), and BSID-III cognitive (left column) and language scores (right column) at 2 years of age.

Table 1Baseline Characteristics of ELBW Infants.^a

Characteristic	ELBW Infants (N = 36)
Maternal Age, years	28.3 (5.4)
Maternal hypertension, n (%)	12 (33%)
Antenatal steroids (completed full course) n (%)	21 (58%)
Gestational age, weeks	25.6 (1.5)
Birth weight, grams	760.3 (145.6)
Male sex, n (%)	19 (53%)
Apgar score <5 at 5 min.	7 (19%)
Late-onset sepsis, n (%)	24 (67%)
Postnatal steroids for BPD, n (%)	8 (22%)
Duration of mechanical ventilation, median days (IQR)	26 (2–58)
Surgery requiring general anesthesia, n (%)	8 (22%)
Abnormal cranial ultrasound in first 28 days, n (%)	12 (33%)
Mild-moderately abnormal MRI at term, n (%)	22 (63%)
Postmenstrual age at MRI, weeks	38.3 (2.1)

^a All values are mean (SD), unless otherwise noted

Table 2

Correlations Between DEHSI Volume, MD, AD, and RD in the Centrum Semiovale and BSID-III Language and Cognitive at 2 Years of Age in ELBW Infants.

DEHSI	Pearson Correlation (coefficient)		Linear Regression (R ²)	
	Language	Cognitive	Language	Cognitive
<i>Volume</i>				
	-0.55 (P=<.001)	-0.58(P=<.001)	29.8% (P=<.001)	33.4% (P=<.001)
<i>Mean diffusivity</i>				
MD mean	-0.07 (P=0.67)	-0.15 (P=0.38)	0.5% (P=0.67)	2.3% (P=0.38)
MD variance	0.04 (P=0.80)	-0.14 (P=0.41)	0.2% (P=0.80)	2.1% (P=0.41)
MD sum	-0.57 (P=<.001)	-0.59 (P=<.001)	32.2% (P=<.001)	34.7% (P=<.001)
<i>Axial diffusivity</i>				
AD mean	-0.09 (P=0.59)	-0.11(P=0.51)	0.9% (P=0.59)	1.3% (P=0.51)
AD variance	0.02 (P=0.90)	-0.05 (P=0.78)	0.1% (P=0.90)	0.2% (P=0.78)
AD sum	-0.58 (P=<.001)	-0.59 (P=<.001)	33.1% (P=<.001)	34.5% (P=<.001)
<i>Radial diffusivity</i>				
RD mean	-0.04 (P=0.84)	-0.12 (P=0.49)	0.1% (P=0.84)	1.4% (P=0.49)
RD variance	-0.01 (P=0.95)	-0.18 (P=0.29)	0.0% (P=0.95)	3.3% (P=0.29)
RD sum	-0.56 (P=<.001)	-0.59 (P=<.001)	31.6% (P=<.001)	34.7% (P=<.001)

DEHSI – diffuse excessive high signal intensity; MD – mean diffusivity; AD – axial diffusivity; RD – radial diffusivity

Table 3

Differences in DEHSI volume, MD sum, AD sum, and RD sum Measures in ELBW Infants with Normal and Low BSID-III Scores.^a

	Bayley Score 90	Bayley Score <90	P Value
<i>Cognitive Score</i>			
DEHSI volume	729.5 (204.0)	1013.6 (144.9)	<0.001
MD sum	0.335 (0.096)	0.479 (0.063)	<0.001
AD sum	0.369 (0.105)	0.524 (0.069)	<0.001
RD sum	0.318 (0.091)	0.457 (0.060)	<0.001
<i>Language Score</i>			
DEHSI volume	693.7 (213.9)	903.2 (186.3)	0.004
MD sum	0.321 (0.102)	0.419 (0.092)	0.005
AD sum	0.352 (0.110)	0.462 (0.099)	0.004
RD sum	0.306 (0.098)	0.397 (0.089)	0.006

^a All values are mean (SD)

DEHSI – diffuse excessive high signal intensity; MD – mean diffusivity; AD – axial diffusivity; RD – radial diffusivity

Table 4

Bayley Scores at 2 Years in ELBW Infants with Subjective Readings and Automated Objectively Diagnosed DEHSI on MRI at Term.^a

BSID-III Score	No or Mild DEHSI	Moderate DEHSI	Severe DEHSI	P Value
<i>Subjective</i>	<i>N = 19</i>	<i>N = 16</i>	<i>N = 1</i>	
Cognitive	95.3 (11.5)	97.2 (13.5)	90	0.802
Language	89.2 (14.8)	91.8 (18.8)	100	0.794
<i>Objective</i>	<i>N = 9</i>	<i>N = 18</i>	<i>N = 9</i>	
Cognitive	105.0 (8.7)	96.4 (11.9)	86.1 (8.6)	0.002
Language	102.1 (9.2)	90.7 (15.2)	77.8 (16.0)	0.004

^a All values are mean (SD), except for subjective severe DEHSI category (actual scores of one patient)