Thirteen-Year Outcomes in Very Preterm Children Associated with Diffuse Excessive High Signal Intensity on Neonatal Magnetic Resonance Imaging

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Objective To investigate the association between white matter diffuse excessive high signal intensity (DEHSI) on neonatal magnetic resonance imaging in very preterm infants and neurobehavioral outcomes at the age of 13 years.

Study design Magnetic resonance images of very preterm children (<30 weeks gestational age or <1250 g birth weight) were evaluated at term-equivalent age with DEHSI classified into 5 grades. Additionally, visibility of the posterior periventricular crossroads was assessed. General intelligence, memory, attention, executive function, motor abilities, and behavior were examined in 125 children at age 13 years and related to DEHSI grades using linear regression.

Results DEHSI was detected in 93% of infants; 21% grade 1, 22% grade 2, 32% grade 3, and 18% grade 4. Neurobehavioral outcomes were similar for all DEHSI groups. There was weak evidence that higher DEHSI grades related to higher verbal IQ and attention and that lower DEHSI grades related to better planning ability. Adjustment for gestational age, birth weight standard score, and sex further weakened these effects. Only 12 children had invisible posterior crossroads and showed slightly poorer outcomes at 13 years of age.

Conclusions There was little evidence that neonatal DEHSI serves as a sensitive biomarker for later impairment. Further investigation on the importance of invisible posterior periventricular crossroads in larger samples is needed. *(J Pediatr 2019;206:66-71).*

Although survival rates of very preterm infants (<32 weeks of gestation) have increased significantly owing to enhanced neonatal care, preterm birth is associated with neonatal brain injury, in particular to the white matter.[1] Although focal cystic periventricular lesions are relatively rare, diffuse white matter abnormalities are the most common neuropathology found in very preterm infants.[1] Furthermore, diffuse excessive high signal intensity (DEHSI) with increased signal intensity in the white matter on T2-weighted magnetic resonance imaging (MRI) around term-equivalent age has been reported in approximately 55%-75% of infants born very preterm[2] and 75%-80% of infants born extremely preterm.[3] DEHSI can occur in isolation or in addition to other white matter changes, including reduced volume, cystic lesions, and delayed myelination.[4] There has been debate as to whether DEHSI reflects brain pathology serving as a biomarker for later neurodevelopment[5] or alterations in maturational characteristics reflecting a developmental phenomenon.[2,6-8]

White matter alterations on neonatal MRI have been associated with consequences on cognition, motor development, and behavior in very preterm children.[9,10] Cognitive, motor, and behavioral problems after preterm birth remain a significant burden.[11] It is, therefore, important to determine precisely which findings on neonatal MRI serve as predictors of long-term outcome in very preterm children, to provide prognostic information for caregivers and families. Although some studies have reported that DEHSI is associated with a worse outcome,[4,12-14] the balance of the evidence suggests no relationship with outcome.[2,7,8,15-17] To date, no study has reported associations between DEHSI and outcome beyond early school age, and there is a lack of studies assessing specific cognitive domains, including memory, attention, and executive function. Thus, the aim of this study was to investigate the associations between neonatal DEHSI and neurobehavioral outcomes in very preterm 13-year-olds. We hypothesized that DEHSI would not be strongly related to neurobehavioral outcome.

MRI	Magnetic resonance imaging
DEHSI	Diffuse excessive high signal intensity

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Methods

Participants were very preterm infants (gestational age of <30 weeks and/or birth weight of <1250 g) admitted to the Royal Women's Hospital, Melbourne, between July 2001 and December 2003 and recruited into a prospective longitudinal cohort study called the Victorian Infant Brain Study. Of 348 eligible very preterm infants admitted to the neonatal nursery, 224 children without genetic or congenital abnormalities likely to interfere with development (eg, craniosynostosis, septo-optic dysplasia) were recruited. Two hundred and nine infants underwent MRI at term-equivalent age (40 weeks gestational age ± 2 weeks). Of those, 49 infants were excluded owing to limited quality of the T2-weighted sequences (n = 24), major cerebral injury seen on term-equivalent MRI (n = 15; 3 with cystic periventricular leukomalacia, 2 with extensive cerebral hemorrhagic lesions, 9 with periventricular hemorrhagic infarction, and 1 with treated posthemorrhagic ventricular dilation), and congenital anomalies (n = 10), resulting in usable neonatal MRI data in 160 infants. Children in the Victorian Infant Brain Study cohort have been followed at 2, 5, 7, and 13 years. The present study included all children who had usable neonatal MRI data and who were assessed at the 13-year follow-up. This study was approved by the Human Research and Ethics Committees of the Royal Women's Hospital and the Royal Children's Hospital, and informed written consent was obtained from the parents at all time points.

MRI

MRIs were obtained on a 1.5T Signa LX EchoSpeed system (GE Healthcare Milwaukee, Wisconsin) without any sedation, including (1) a 3-dimensional spoiled gradient-recalled echo sequence (0.8- to 1.6-mm coronal sections; flip angle, 45°; repetition time, 35 ms; echo time, 9 ms; field of view, 210 × 157.5 mm; matrix, 256 × 192, interpolated 256 × 256) and (2) a double-echo (proton-density and T2-weighted) spin-echo sequence (1.7- to 3.0-mm axial sections; flip angle, 90°; repetition time, 4000 ms; echo time, 60 and 160 ms; field of view, 220 × 165 mm; matrix, 256 × 192, interpolated 512 × 512; interleaved acquisition).

MRI Analysis

Grading of DEHSI was conducted by 1 investigator trained in fetal and preterm MRI and blinded to the clinical data. Grading was based on severity and extent of signal intensity and classified into 5 grades: 0 (no DEHSI throughout the white matter), 1 (DEHSI visible only within the crossroads), 2 (DEHSI visible in one region additional to the crossroads), 3 (DEHSI visible in two additional regions), and 4 (DEHSI visible in 3 additional regions [extensive white matter]). (For an illustration of the grades refer to Kidokoro et al.[17]).

For infants with DEHSI grades 2-4, we additionally assessed whether the margins of the posterior periventricular crossroads were visible. Healthy variations of immature white matter typical for this age of assessment are visible as high signal intensity in the white matter of the posterior periventricular crossroads[18] (**Figure 1**; available at www.jpeds.com). If crossroads were visible, this indicated typical signal intensity; widespread signal intensity such that the periventricular crossroads were invisible indicated signal intensity beyond the healthy maturational variations.

The interobserver agreement on the DEHSI grade was assessed in 15 infants by 2 authors using kappa statistics. The observers showed complete agreement in 10 infants, a difference of 1 grade in 4, and a difference of 2 grades in 1 infant ($\kappa = 0.58$). Test-retest agreement in the 15 infants was perfect ($\kappa = 1$).

Neurobehavioral Outcome Measures

At the 13-year follow-up, general intelligence was estimated with the Kaufman Brief Intelligence Test, Second Edition,[19] of which the Kaufman Brief Intelligence Test IQ composite, verbal and nonverbal standard scores (100 ± 15) are reported. Short-term memory was evaluated using the digit recall subtest and working memory was investigated using the backward digit recall subtest (100 ± 15) of the Working Memory Test Battery for Children.[20] Attention was assessed using subtests from the Test of Everyday Attention for Children,[21] including Score! (sustained attention) and map mission (selective attention, 10 ± 3). Executive function was evaluated using the subtests from the Behavioural Assessment of the Dysexecutive System for Children.[22] The Zoo Map test captures the ability to plan and execute a specific eight-location sequence in accordance with several rules (Zoo Map total score, 10 ± 3) and the Six Part Test examines planning, task scheduling and performance monitoring skills (Six Part total score, 10 ± 3). The behavioral manifestations of children's executive control functions were assessed with the Behavior Rating Inventory of Executive Function,[23] a parent-completed rating scale including a Global Executive Composite, a Behavioral Regulation Index, and a Metacognition Index (50 ± 10; high scores reflect worse outcome). Motor function was evaluated with the Movement Assessment Battery for Children 2.[24] A total composite score, derived from the summarized subtest standard scores, and manual dexterity, aiming and catching, as well as a balance component scores are reported (10 ± 3). Higher scores reflected better functional outcome in all of these measures except the Behavior Rating Inventory of Executive Function parent rating, where higher scores reflected a worse outcome.

Statistical Analyses

Baseline characteristics were described for participants with differing degrees of DEHSI as proportions for categorical data and mean ± SD for continuous data.

Because our sample included a number of multiple births, regression models were fitted by using generalized estimating equations with an exchangeable correlation structure and are reported with robust standard errors to allow for nonindependence of multiples.[25] Associations between DEHSI and neurobehavioral outcome were examined using linear regression with separate models for each predictor–outcome combination. Analyses were repeated adjusting for gestational age, female sex, and birth weight SD score, variables known to be associated with improvements in most of the outcomes studied.

Further, for infants with DEHSI grades 2-4, linear regression models were fitted to examine differences in neurobehavioral outcomes between those children who had visible and those who had invisible posterior crossroads in their neonatal scan. Analyses were conducted by using SPSS version 24 (IBM SPSS Statistics, IBM Corporation, Armonk, New York) and Stata 14.2 (Stata Corp, College Station, Texas). Interpretation of the findings was based on overall patterns and magnitude of differences rather than individual *P* values.[26]

Results

Patient Characteristics

Of 160 preterm infants who were eligible and had usable neonatal MRI data, 125 children had usable MRI data and follow-up data at 13 years (mean age, 13.3 ± 0.4 years). Thirty-five children were not assessed at the 13-year follow-up (unable to contact, n = 8; withdrawn, n = 8; declined to participate, n = 18; died, n = 1). Participants' neonatal characteristics are summarized in **Table I** (available at www.jpeds.com). Participants and nonparticipants had similar perinatal/neonatal characteristics (**Table II**; available at www.jpeds.com).

Most infants had some grade of DEHSI visible on their term-equivalent MRI (**Table I**). The neonatal characteristics of the DEHSI groups were generally comparable, but the DEHSI grade 0 group was small (n = 9) and tended to have a lower mean birth weight.

Neurobehavioral Outcomes after DEHSI

Neurobehavioral outcomes for each DEHSI grade are summarized in **Table III**. Outcomes were broadly similar between groups. Regression analysis yielded weak evidence for linear relationships between DEHSI and verbal IQ, selective attention, and planning ability (**Table IV**), but **Figure 2** demonstrates that the relationships were more complex and not clinically meaningful. Adjusting for gestational age, birth weight SD score, and sex decreased the strength of the evidence for the linear associations between DEHSI grade and most outcomes; only the linear relationship with planning ability retained some evidence to support it.

Neurodevelopmental Outcomes in Invisible Posterior Crossroads

Among the 90 children with grades 2-4 DEHSI, 12 had invisible posterior crossroads (5 in grade 3 and 7 in grade 4 DEHSI), and 78 had visible posterior crossroads (28/28 children who had grade 2 DEHSI had visible crossroads, 35/40 children with grade 3 DEHSI and 15/22 with grade 4 DEHSI). There was weak evidence that invisibility of posterior crossroads was related to worse neurobehavioral outcome, with lower scores on tests of intelligence, memory, attention, and executive function, and higher scores on the behavioral questionnaire compared with children with visible crossroads in 15 of the 16 variables (**Table V**).

Discussion

It is established that DEHSI is visible on neonatal MRI in a high proportion of very preterm children. There is ongoing debate as to whether DEHSI serves as a biomarker for later neurodevelopmental outcome. To date, results are inconsistent and there are no reports on long-term outcomes in very preterm adolescents that allow for a reliable examination of specific areas of cognitive function, such as executive function.[27] In our sample of 125 very preterm children without severe cerebral injuries at term-equivalent age, there was little evidence

Table III. Neurobehavioral outcomes at 13 years of age for children in each grade of DEHSI

	Grade 0		Grade 1		Grade 2		Grade 3		Grade 4		Total	
Neurobehavioral domains	**n**	**Mean ± SD**	**n**	**Mean ± SD**	**n**	**Mean ± SD**	**n**	**Mean ± SD**	**n**	**Mean ± SD**	**n**	**Mean ± SD**
General intelligence												
IQ composite	9	91.9 ± 20.7	26	97.9 ± 14.5	28	101.1 ± 16.7	40	104.8 ± 18.1	22	101.3 ± 16.6	125	101.0 ± 17.1
Verbal IQ	9	92.6 ± 16.4	26	95.7 ± 13.2	28	101.2 ± 15.0	40	105.2 ± 15.7	22	100.2 ± 15.7	125	100.5 ± 15.4
Nonverbal IQ	9	92.4 ± 24.1	26	100.2 ± 15.7	28	100.1 ± 17.7	40	102.6 ± 18.3	22	101.9 ± 16.9	125	100.7 ± 17.8
Memory												
Short-term memory, digit span forward	9	95.9 ± 21.1	26	97.4 ± 15.4	28	98.6 ± 20.1	40	92.4 ± 14.5	22	93.3 ± 16.5	125	95.3 ± 16.8
Working memory, digit span backwards	9	89.3 ± 14.1	26	94.2 ± 15.4	28	95.0 ± 13.0	40	89.1 ± 12.0	22	94.6 ± 17.4	125	92.5 ± 14.2
Attention												
Sustained attention, Score!	9	7.4 ± 4.3	26	8.9 ± 3.5	28	8.4 ± 3.7	40	7.8 ± 3.6	22	7.6 ± 3.6	125	8.1 ± 3.6
Selective attention, map mission	9	5.4 ± 3.5	26	6.4 ± 2.9	27	6.5 ± 3.3	40	6.7 ± 3.4	21	8.4 ± 2.9	123	6.8 ± 3.2
Executive function												
Planning, zoo map 1	7	8.0 ± 3.3	25	7.7 ± 3.6	26	8.8 ± 3.6	39	7.7 ± 3.3	22	8.2 ± 3.6	119	8.0 ± 3.5
Planning and monitoring, 6 parts test	7	8.1 ± 2.6	25	8.6 ± 3.3	26	6.6 ± 3.0	39	6.4 ± 2.4	22	8.8 ± 3.2	119	7.5 ± 3.0
Motor function												
Global composite	7	8.1 ± 3.6	25	8.6 ± 3.0	26	8.4 ± 2.2	35	9.0 ± 3.0	21	9.1 ± 3.0	114	8.8 ± 2.9
Manual dexterity	7	7.7 ± 2.6	25	7.6 ± 2.9	26	7.8 ± 2.7	37	8.7 ± 3.2	21	8.5 ± 3.4	116	8.2 ± 3.0
Aiming and catching	8	7.9 ± 3.4	26	9.6 ± 3.7	27	10.6 ± 3.4	35	9.6 ± 3.2	21	11.2 ± 2.9	117	10.0 ± 3.4
Balance	7	9.6 ± 4.2	25	9.5 ± 2.4	26	8.6 ± 2.4	35	9.4 ± 3.1	21	8.9 ± 2.9	114	9.2 ± 2.8
Parent Rating Behavior*												
Global executive composite	7	59.0 ± 11.9	23	56.9 ± 12.3	26	55.3 ± 12.8	36	52.7 ± 11.2	20	55.5 ± 15.2	112	55.0 ± 12.5
Behavioral regulation index	7	58.0 ± 13.3	23	53.7 ± 10.2	26	54.5 ± 14.8	36	51.6 ± 11.1	20	56.2 ± 18.7	112	53.9 ± 13.5
Metacognition index	7	58.7 ± 13.3	23	58.1 ± 13.0	26	55.1 ± 11.9	36	52.9 ± 11.4	20	54.4 ± 12.7	112	55.1 ± 12.2

*Higher scores reflective of more behavioral difficulties.

Table IV. Association between DEHSI and neurobehavioral outcomes in very preterm children

Neurobehavioral outcome	n	Estimate (95% CI)	*P* value	Adjusted estimate (95% CI)†	Adjusted *P* value†
General intelligence					
IQ composite	125	2.5 (0.0 to 4.9)	.05	1.8 (–0.9 to 4.4)	.19
Verbal IQ	125	2.6 (0.4 to 4.9)	.022	2.2 (–0.2 to 4.6)	.07
Nonverbal IQ	125	1.7 (–1.1 to 4.5)	.24	1.0 (–1.8 to 3.7)	.49
Memory					
Short-term memory, digit span forward	125	–1.3 (–3.8 to 1.2)	.30	–2.2 (–4.4 to 0.1)	.06
Working memory, digit span backwards	125	–0.1 (–2.4 to 2.2)	.94	–0.8 (–2.9 to 1.3)	.46
Attention					
Sustained attention, Score!	125	–0.3 (–0.8 to 0.3)	.35	–0.4 (–1.0 to 0.2)	.16
Selective attention, map mission	123	0.6 (0.1 to 1.0)	.020	0.5 (–0.0 to 1.00)	.06
Executive function					
Planning, zoo map 1	119	0.0 (–0.5 to 0.6)	.93	–0.1 (–0.6 to 0.5)	.75
Planning and monitoring, 6 parts test	119	–0.7 (–1.2 to –0.1)	.023	–0.6 (–1.1 to –0.1)	.027
Motor function					
Global composite	114	0.2 (–0.3 to 0.7)	.38	0.1 (–0.4 to 0.6)	.77
Manual dexterity	116	0.4 (–0.1 to 0.9)	.10	0.3 (–0.2 to 0.8)	.29
Aiming and catching	117	0.5 (–0.5 to 1.0)	.08	0.3 (–0.3 to 0.8)	.31
Balance	114	–0.1 (–0.6 to 0.4)	.64	–0.2 (–0.6 to 0.3)	.49
Behavioral executive function*					
Global executive composite	112	–1.1 (–3.5 to 1.3)	.37	–0.9 (–3.2 to 1.4)	.45
Behavioral regulation index	112	0.4 (–1.7 to 2.5)	.70	0.7 (–1.7 to 2.9)	.57
Metacognition index	112	–1.5 (–3.8 to 0.8)	.21	–1.5 (–4.0 to 1.0)	.24

Estimates of regression coefficients from separate linear regression models fitted using generalized estimating equations to allow for clustering of twins.
Estimates and 95% CI from linear regression models fitted using generalized estimating equations with an exchangeable correlation structure to account for clustering owing to multiple births.
*Higher scores reflective of a greater amount of reported behavioral difficulties.
†Adjusted for gestational age, female sex, and birthweight SD score.

that the extent of DEHSI was systematically related to poorer neurobehavioral outcome, including intelligence, memory, attention, executive function, motor abilities, and behavior at 13 years of age.

Our findings are in line with studies examining associations between DEHSI and outcome on developmental tests in preschoolers[2,6-8,15] and on a broader range of tests in early school-age children.[16] Nevertheless, some studies have found DEHSI to be related to early development in very preterm and extremely low birth weight (<1000 g) preschoolers.[4,12] Further, a sample of high-risk preterm infants with DEHSI performed nearly ten points lower (0.67 SD) on Full-Scale IQ at 6 years of age compared with those without DEHSI.[13] Additional follow-up of these groups into late childhood is important to determine whether these group differences persist.

The lack of systematic associations between DEHSI assessed based on the presence and severity of signal intensity in our relatively large cohort followed to 13 years suggests that neonatal DEHSI has little predictive value for neurodevelopmental outcome. Thus, our findings suggest that DEHSI reflects a transient developmental phenomenon or that the immature brain has the capacity for compensation. To predict functional outcome, a more comprehensive scoring system of neonatal MRI combining assessments of the nature and extent of white matter signal abnormality, loss of volume of periventricular white matter, the extent of cystic abnormalities, ventricular dilatation, and the thinning of the corpus callosum may be more useful.[9,28] Such a scoring system has been used to predict poorer cognitive, motor and neurosensory impairment in very preterm 2-year-olds,[28] and poorer IQ,

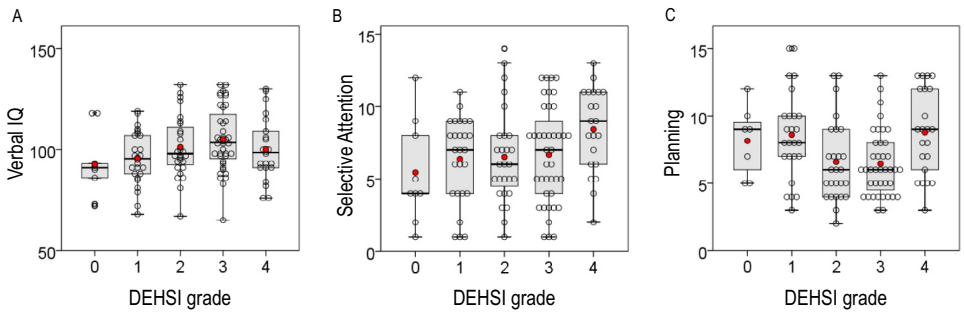

Figure 2. Neurobehavioral outcomes at 13 years for children in each DEHSI grade. Scatterplots showing individual data points (*empty circles*), group mean (*red dots*), overlaid with boxplots indicating first and third quartiles (*bottom and top of box*), the median (*band inside the box*) and maximum 1.5 interquartile range (*end of whiskers*). Results are shown for **A,** verbal IQ, **B,** selective attention and **C,** planning ability.

Table V. Neurobehavioral outcome in children with invisible vs visible posterior crossroads

Neurobehavioral outcomes	Invisible mean	SD	n	Visible mean	SD	n	Mean difference (95% CI)	*P*
General intelligence								
IQ Composite	98.8	15.2	12	103.4	17.5	78	−3.5 (−12.2 to 5.1)	.42
Verbal IQ	96.3	14.1	12	103.7	15.5	78	−6.5 (−14.8 to 1.8)	.13
Nonverbal IQ	101.6	16.6	12	101.6	17.9	78	−1.0 (−9.9 to 7.9)	.83
Memory								
Short-term memory, digit span forward	85.8	19.3	12	95.9	16.2	78	−9.8 (−20.6 to 1.1)	.08
Working memory, digit span backwards	87.5	12.9	12	93.0	14.0	78	−6.4 (−14.4 to 1.7)	.12
Attention								
Sustained attention—Score!	7.6	4.3	12	8.0	3.5	78	−0.4 (−2.8 to 2.0)	.75
Selective attention, map mission	6.6	3.2	11	7.1	3.3	77	−0.7 (−2.7 to 1.3)	.50
Executive function								
Planning, zoo map 1	7.3	3.6	12	8.3	3.4	75	−1.1 (−3.1 to 1.0)	.31
Planning and monitoring, 6 parts test	6.8	2.9	12	7.1	3.0	75	−0.5 (−1.9 to 1.1)	.56
Motor function								
Global composite	8.9	3.6	11	8.9	2.7	71	−0.2 (−2.3 to 1.9)	.86
Manual dexterity	8.5	3.8	11	8.4	3.0	73	−0.5 (−2.8 to 1.8)	.70
Aiming and catching	10.6	3.8	11	10.3	3.2	72	0.3 (−2.0 to 2.5)	.92
Balance	8.4	3.0	11	9.1	2.8	71	−0.8 (−2.7 to 1.0)	.37
Behavioral executive function*								
Global executive composite	58.5	13.6	10	53.4	12.6	72	2.8 (−5.0 to 10.5)	.49
Behavioral regulation index	55.1	15.2	10	53.2	14.3	72	1.5 (−6.5 to 9.5)	.71
Metacognition index	59.2	12.3	10	53.6	11.6	72	4.5 (−3.0 to 12.0)	.24

Estimates of regression coefficients from separate linear regression models fitted using generalized estimating equations to allow for clustering of twins.
*Higher scores reflective of more behavioral difficulties.

academic, and motor outcomes at 7 years of age, beyond the effect of other perinatal and neonatal variables.[9]

Children with grade 0 DEHSI had lower mean scores on some of the reported measures. However, this group comprised only 9 children, which limits the generalizability of this finding and limits speculation about whether DEHSI might just be a normal variant in very preterm children at term-equivalent age.

We also investigated the presence of high signal intensity within the periventricular posterior crossroads, which form important intersections for projection and corticocortical fiber pathways.[29] In the same sample of children assessed for the present study, invisible posterior crossroads were associated with a reduction in cognitive development and an increased risk of cognitive delay at age 2 years.[17] In the present study, there was some evidence that 13-year-old children with invisible crossroads showed worse outcome across a range of neurobehavioral measures, although the mean differences were nonsignificant and smaller than at the 2-year follow-up. Although our results may be suggestive of invisible periventricular posterior crossroads being a possible biomarker of later neurodevelopmental outcome, our study sample with invisible crossroads was small (n = 12) and further studies in other cohorts, with larger samples are required to further investigate this relationship.

Methodological limitations of the DEHSI rating limit the interpretation of our findings. It has been suggested that T2-weighted sequences should be optimized using fluid-attenuated inverse recovery for a better distinction between DEHSI and cerebrospinal fluid, because they may appear in the same intensity distribution in conventional T2 images.[30] Furthermore, the signal intensity of T2-weighted images is susceptible to magnetic field inhomogeneity. Increased signal intensity caused by field inhomogeneity may be confused with DEHSI.[31] Hence, T2 relaxometry is suggested because it is thought to provide an improved distinction between cerebrospinal fluid and DEHSI over that of conventional T2-weighted imaging.[31]

Scoring DEHSI is potentially variable and subjective in nature.[16] In the present study, scoring was done by 1 physician only. In a subset of the present study, however, interrater and intrarater agreement were moderate. This difference may have contributed to the lack of associations between DEHSI and neurobehavioral outcomes in the present study. Further studies should examine the predictive value of automated DEHSI scoring for long-term neurobehavioral outcomes.

Although we had some attrition, compared with other studies, our sample is large and to the best of our knowledge, no other study has reported relationships between DEHSI and such a broad range of cognitive and motor outcomes in early adolescence.

The presence of qualitatively defined DEHSI on term-equivalent MRI does not seem to be useful as a predictor of long-term neurobehavioral outcomes in very preterm children. The predictive value of the less common finding of a lack of visibility of the posterior periventricular crossroads with DEHSI needs further investigation. ■

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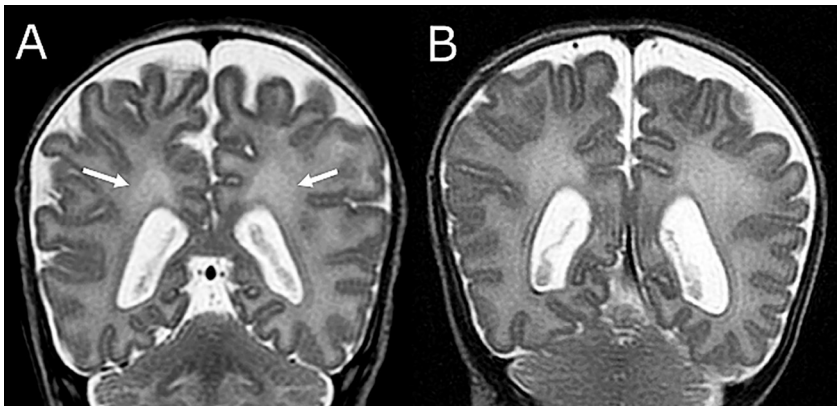

Figure 1. Samples of visible (typical) and invisible (atypical) posterior periventricular crossroads. **A,** High signal intensity is visible within the crossroads (*arrows*). **B,** Posterior periventricular crossroads are invisible because of widespread homogeneous high signal intensity of the entire cerebral white matter surrounding the crossroads.

Table I. Participant characteristics

	Grade 0 (n = 9)	Grade 1 (n = 26)	Grade 2 (n = 28)	Grade 3 (n = 40)	Grade 4 (n = 22)	Total (n = 125)
Gestational age at birth, weeks	26.1 ± 1.9	26.6 ± 1.4	27.8 ± 2.2	27.9 ± 2.0	27.7 ± 1.7	27.5 ± 1.9
Postmenstrual age at MRI, weeks	40.4 ± 1.5	40.1 ± 1.9	39.9 ± 1.0	40.5 ± 1.5	40.5 ± 1.2	40.3 ± 1.5
Birthweight, g	789 ± 183	875 ± 236	967 ± 228	1007 ± 209	985 ± 214	951 ± 225
Birthweight z-score	–0.5 ± 1.3	–0.5 ± 0.9	–0.8 ± 1.0	–0.6 ± 0.9	–0.6 ± 0.9	–0.6 ± 0.9
Exposure to antenatal corticosteroids	8 (89)	25 (96)	26 (93)	34 (85)	19 (86)	112 (90)
Exposure to postnatal corticosteroids	2 (22)	3 (12)	2 (7)	3 (8)	2 (9)	12 (10)
Proven sepsis	4 (44)	11 (42)	16 (57)	14 (35)	11 (50)	56 (45)
Proven necrotizing enterocolitis	1 (11)	2 (8)	0	3 (8)	2 (9)	8 (6)
Bronchopulmonary dysplasia	4 (44)	10 (39)	10 (36)	14 (35)	6 (27)	44 (35)
Grade III-IV intraventricular hemorrhage*	0	1 (4)	0	1 (3)	0	2 (2)
Cystic periventricular leukomalacia*	0	1 (4)	0	1 (3)	1 (5)	3 (2)
Patent ductus arteriosus	5 (56)	17 (65)	10 (36)	18 (45)	12 (54)	62 (50)
Female sex	6 (67)	13 (50)	10 (36)	19 (48)	10 (46)	58 (47)
Singleton	6 (67)	9 (35)	16 (57)	22 (55)	16 (73)	69 (55)

Values are mean ± SD or n (%).
Bronchopulmonary dysplasia defined as oxygen dependency at 36 weeks of gestation.
*Detected on neonatal ultrasound examination.

Table II. Neonatal characteristics

	Participants (n = 125)	Nonparticipants (n = 99)	Mean difference (95% CI)	*P* value
Gestational age at birth, weeks	27.5 ± 1.9	27.5 ± 1.8	0 (–0.5 to 0.4)	.90
Postmenstrual age at MRI, weeks	40.3 ± 1.5	40.2 ± 2.0	0.1 (–0.4 to 0.5)	.82
Birthweight—g	951 ± 225	973 ± 226	–30.5 (–85.3 to 24.3)	.27
Birthweight z-score	–0.6 ± 0.9	–0.5 ± 0.9	–0.1 (–0.4 to 0.1)	.28
Exposure to antenatal corticosteroids	112 (90)	86 (90)	0.1 (0 to 0.2)	.21
Exposure to postnatal corticosteroids	12 (10)	9 (9)	0 (–0.1 to 0.1)	.75
Proven sepsis	56 (45)	42 (42)	0.4 (–0.1 to 0.2)	.53
Proven necrotizing enterocolitis	8 (6)	2 (2)	0.1 (–0.1 to 0.2)	.28
Bronchopulmonary dysplasia	44 (35)	31 (31)	0 (–0.3 to 0.2)	.69
Grade III-IV intraventricular hemorrhage*	2 (2)	6 (6)	0 (0 to 0.1)	.09
Cystic periventricular leukomalacia*	3 (2)	6 (6)	0 (–0.1 to 0)	.19
Patent ductus arteriosus	62 (50)	48 (49)	0.1 (–0.1 to 0.2)	.37
Female sex	58 (47)	52 (53)	0 (–0.2 to 0.1)	.47
Singleton	69 (55)	61 (62)	0.1 (–0.1 to 0.2)	.40

Values are mean ± SD or n (%) unless otherwise noted.
Estimates of regression coefficients from separate linear regression models fitted using generalized estimating equations to allow for clustering of twins.
Bronchopulmonary dysplasia defined as oxygen dependency at 36 weeks of gestation.
*Detected on neonatal ultrasound examination. Thirty-five of the nonparticipating children had DEHSI scoring with 11% showing grade 0, 40% grade 1, 11% grade 2, 37% grade 3, and none grade 4.