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Automated brain MRI metrics in the EPIRMEX cohort of preterm newborns: Correlation with the neurodevelopmental outcome at 2 years

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ABSTRACT

Purpose: The purpose of this study was to identify in the EPIRMEX cohort the correlations between MRI brain metrics, including diffuse excessive high signal intensities (DEHSI) obtained with an automated quantitative method and neurodevelopmental outcomes at 2 years.
Materials and methods: A total of 390 very preterm infants (gestational age at birth ≤ 32 weeks) who underwent brain MRI at term equivalent age at 1.5T ($n = 338$) or 3T ($n = 52$) were prospectively included. Using a validated algorithm, automated metrics of the main brain surfaces (cortical and deep gray matter, white matter, cerebrospinal fluid) and DEHSI with three thresholds were obtained. Linear adjust regressions were performed to assess the correlation between brain metrics with the ages and stages questionnaire (ASQ) score at 2 years.
Results: Basal ganglia and thalami, cortex and white matter surfaces positively and significantly correlated with the global ASQ score. For all ASQ sub-domains, basal ganglia and thalami surfaces significantly correlated with the scores. DEHSI was present in 289 premature newborns (74%) without any correlation with the ASQ score. Metrics of DEHSI were greater at 3T than at 1.5T.
Conclusion: Brain MRI metrics obtained in our multicentric cohort correlate with the neurodevelopmental outcome at 2 years of age. The quantitative detection of DEHSI is not predictive of adverse outcomes. Our automated algorithm might easily provide useful predictive information in daily practice.

Abbreviations: ASQ, Age and stage questionnaire; BGT, Basal ganglia and thalami; DEHSI, Diffuse excessive high signal intensity; GA, Gestational age; MRI, Magnetic resonance imaging; SD, Standard deviation; TEA, Term equivalent age; WA, Week of amenorrhea.

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1. Introduction

Owing to progress in neonatal care, the preterm newborn survival rate has increased during recent years. However, prematurity remains a leading cause of morbidity and conveys high risk of developmental delay [1]. Clinical perinatal factors related to adverse outcomes have been identified, such as lower gestational age (GA) [2], intrauterine growth restriction [3], bronchopulmonary dysplasia [4], infection [5], necrotizing enterocolitis, severe brain lesions on cranial ultrasound or on brain magnetic resonance imaging (MRI) [6], but are not yet sufficient to predict accurately all disability developments. Early identification of newborns at risk of later developmental disabilities may increase access to specific evaluation and subsequent adapted care, potentially influencing the course of otherwise persistent difficulties.

Brain MRI is a very powerful complementary tool to diagnose and follow injury in preterm infants [7]. Periventricular leukomalacia associated with cystic lesions, white matter reduced volume, stigmata of hemorrhage and delayed myelination are possible brain sequelae of prematurity.

Simple brain metric such as biparietal width or interhemispheric distance did not reliably predict neurodevelopmental outcome in a cohort with low prevalence of high-grade brain injury [8]. Associations of conventional brain MRI at term equivalent age (TEA) with long-term neurodevelopmental impairments in preterm children are of particular interests with high specificity [9,10]. Structural and volumetric MRI at TEA and neurological examinations could predict long-term neuromotor outcome in premature newborns [6,11,12,13]. But neonatal brain MRI segmentation is difficult to perform due to the imaging characteristics of the developing brain (*i.e.*, smaller head size and shorter scanning duration).

Moreover, quantitative analysis of white matter in premature newborns remains a challenging issue [14]. Maalouf et al. have described diffuse excessive high signal intensity (DEHSI) of the white matter in the centrum semiovale on conventional T2-weighted images [15]. Increasing severity of white-matter abnormalities on MRI at term equivalent is associated with poorer performance on the cognitive and psychomotor scales of the BSID-II [16]. When focusing on DEHSI, these results were supported by Dyet et al. [17] and Parikh et al. [18,19]. The prognosis was secondarily controverted. Normal neurologic outcomes were observed at a corrected age of 18 months to 36 months in premature with DEHSI [12,20,21]. Today, the prognostic value of DEHSI is still controversial, ranging from a normal transient feature to a predictive factor for mental retardation [12,13,17,18,19,20,21]. However, apart from Parikh et al. study that has used a T2 relaxometry algorithm to detect white matter abnormality in centrum semiovale, the DEHSI detection was performed with a qualitative visual assessment by one or two observers, in a limited size of cohort.

To address these issues, we have developed a specific algorithm to automatically obtain brain MRI metrics in preterm neonates, based on a mathematical morphology approach with max-tree representations and a supplementary quantitative evaluation of diffuse high signal intensity regions of the white matter on T2 weighted images [22]. It has been already validated using 1.5T and 3T MRI equipments with a high reproducibility and robustness [22].

Using this approach, the aim of our study was to identify in the large EPIRMEX cohort the correlations between MRI brain metrics, including DEHSI and the neurodevelopmental outcomes at 2 years.

2. Materials and methods

2.1. Population

Between June 28th, 2011 and October 31st, 2012, 519 preterm infants from 26 to 31 completed weeks of gestation from 16 university hospital centers in 12 regions were recruited at birth into a national prospective longitudinal cohort study (EPIRMEX cohort study associated with EPIPAGE 2). The inclusion was the same as the EPIPAGE2; eligible participants include all infants liveborn or stillborn between 22 and 31 completed weeks of gestation in all the maternity units in French during the inclusion period. The population eligible for follow-up includes all children alive at discharge from neonatal intensive care or special units or maternity wards whose parents have not declined to participate [23]. Non-inclusion criteria were children with severe karyotypic abnormalities, antenatal severe central nervous system malformations.

All survivors were enrolled for longitudinal follow-up and included in the study at 2 years corrected age if parents consented. Perinatal and maternal details were collected by chart review at the time of recruitment. Ninety-nine patients with incomplete clinical data were excluded from the statistical analysis. Thirty brain MRI at TEA had severe artifacts and were non-interpretable. Three hundred ninety brain MRI with complete clinical data and ages and stages questionnaire (ASQ) score were analyzed. Comparisons between excluded and included patients were performed. Two subgroups have been defined depending on the magnetic field used (1.5 or 3T). The study was approved by the Human Research Ethic Committee (2011-10_9). Written informed parental consent was obtained for all infants.

2.2. MRI protocol

MRI brain scans were performed in natural sleep at TEA (i.e., GA of 39-41 weeks), using a 1.5T or 3T MRI system with a dedicated 8-channel head coil.MR devices with a magnetic field of 1.5T were Philips Achieva®, Philips Intera®, Toshiba MRT 200®, GE SignaHdxt® (General Electric Healthcare), Siemens Avanto®, Siemens Symphony®, and Siemens SymphonyTim® (Siemens Heathineers). The MRI device with a magnetic field of 3T was a Philips Achieva® (Philips Healthcare).

T2 datasets were obtained using an axial T2 morphological sequence (fast spin echo/turbo spin echo with a 90 flip-back pulse); slice thickness, 3 mm; pixel size, 0.39×0.39 mm^2; field of view, 192 mm; repetition time, 6680 ms; echo time, 142 ms; flip angle, 120°. The axial MRI reference plane was the bi-commissural plane.

MRI protocol also included also an axial T2*-weighted sequence, an axial diffusion-weighted sequence ($b = 1000$ s/mm^2), and a three-dimensional T1 MPRage sequence (spatial resolution, $0.8 \times 0.8 \times 1.2$ mm^3; inversion time, 110 ms; repetition time, 2200 ms; echo time, 2.49 ms; flip angle, 8°).

A medical engineer visited all participating centers to check the sequence parameters. The infants were fed, swaddled and had earplugs. No child has received medicated sedation. Throughout the scan, infants were monitored using an apnea monitor and an oxygen saturation probe, and if required, oral sucrose was administered with parental consent.

2.3. Automated brain metrics

2.3.1. Anatomical structures

The previously described validated semi-automated mathematical morphology segmentation method was used by one observer on a single axial T2 section on which the caudate heads, lentiform

nuclei, and thalami were maximally visible, as defined by Kidokoro et al. [24]. A quality control was performed by a secondary blind observer to determine the most appropriate slice. A qualitative assessment of the absence of morphologic sequelae of hemorrhage and cystic lesions of the segmented MRI axial slice was performed by a pediatric radiologist prior to segmentation.

The segmentation method sequentially extracted each brain tissue from the axial T2-weighted neonatal brain images. The algorithm relied on some morphological methods, notably the max-tree representation proposed by Salembier et al. [25], which is a hierarchical representation of the image based on threshold decomposition. First the intracranial cavity was extracted as the region of interest and then the cerebrospinal fluid and ventricles using the max-tree and the context-based energy based on the selection strategy relying on markers. The basal ganglia and thalami (BGT) were extracted using a modified max-tree built. Then the gray matter and white matter were separated from the remaining tissues based on the optimal histogram-based thresholding. White matter hyperintensities (*i.e.*, DEHSI) were segmented using the max-tree and the context-based energy again [22]. Comparisons on the segmentation results on premature scanned at 1.5T and 3T were performed.

2.3.2. Detection and quantification of white matter signal abnormalities (DEHSI)

Within the segmented white matter, DEHSI were automatically detected with three different thresholds of intensity of 80%, 85% and 90% of the maximal signal intensity on MRI (where 100% corresponded to the cerebrospinal fluid intensity signal). The corresponding surfaces were measured in mm^2. A qualitative visual inspection of the segmentation results has been performed by a second observer. No delineation error was reported. The considered method was observed to perform well in the presence of common brain abnormalities in preterm infants, including enlarged ventricles and white matter signal intensity abnormalities. Results of the segmentation were automatically displayed and tabulated. Further analyses were performed on the results obtained on premature newborns scanned at 1.5T and those scanned at 3T.

2.4. Two-year developmental assessment

All parents were invited to attend a developmental assessment at 2 years' corrected age. Children's development was assessed with the second version of the 24-month ASQ [26,27]. Data were analyzed when completed between 22- and 26-months corrected age in children without deafness, blindness, or severe congenital brain malformations. Each questionnaire includes 30 items covering five developmental domains: communication abilities, gross motor skills, fine motor skills, problem solving abilities, and personal-social skills. Each developmental domain comprises 6 items scored on a three-point scale depending on whether the child performs the task: yes (10 points), sometimes (5 points), or not yet (0 points). Responses are summed to give a score of 0 to 60 for each domain and an overall maximum ASQ score of 300 points. Analyses were based on domain specific scores [28].

2.5. Statistical analysis

Qualitative variables were expressed as raw number and percentages. Percentages were reported with their exact 95% binomial confidence intervals. Quantitative variables were expressed as means ± standard deviations (SD) and ranges. Qualitative variables were compared using Chi squared test, and quantitative variables were compared using Student t-test after the evaluation of their distribution by a histogram.

The associations between brain MRI measures with global ASQ score and between BGT and ASQ sub-domains were explored using adjusted linear regression analyses (age of gestation, gender, corrected age during MRI, severe brain lesion such as grade III hemorrhage and cystic periventricular leukomalacia observed at cranial ultrasound). All tests were two sided. A P value < 0.05 was considered to indicate statistical significance. Statistical analyses were performed using R software [29].

3. Results

3.1. Population and MRI

Of the 519 newborn participants included in this study, 489 premature newborns had brain MRI axial slice with normal findings. Nineteen (19/519; 3.66%) had sequelae of hemorrhage, 10 (10/519; 1.93%) had ventricular dilatation and 1 (1/519; 0.19%) had sequelae of cystic periventricular leukomalacia. In all newborns, segmentation was obtained.

Of the 519 newborn participants included in this study, 390 (390/519; 75.14%) newborns had complete clinical data and brain MRI suitable for analysis and DEHSI detection. Participants were similar to excluded patients for all compared perinatal variables (Table 1).

The mean birth weight of our cohort was 1174 ± 339 (SD) g (range: 443–2380 g), the mean adjusted gestational age was 28.57 ± 1.82 (SD) (range: 24–33) weeks of amenorrhea (WA) and the mean corrected age for the MRI at TEA was performed at 39.8 ± 1.40 (SD) WA (range: 38–42 WA).

Distribution and characteristics of newborn scanned at 1.5T (n = 338) and 3T (n = 52) are detailed in Table 1. Fig. 1 shows the flow chart of inclusion and exclusion of patients.

3.2. Two-year developmental assessment

At 2 years of age, 390 (390/519; 75.14%) children completed the ASQ score. The mean overall ASQ score was 221.5 ± 53.4 (SD) (range: 30–300) out of 300 points. The detailed results of the ASQ sub-domains are presented in Table 2. The gender was an important adjusted coefficient: boys had a significantly lower ASQ than girls (linear adjusted coefficient of −16 for the BGT surface associated with the global ASQ score; P = 0.002). There was no difference in the ASQ score of newborns scanned at 1.5T (222 ± 53 [SD]; range: 30–300) or 3T (215 ± 53 [SD]; range: 20–295) (P = 0.404).

3.3. Associations between MRI measures and 2-year development

3.3.1. Brain metrics

Metrics were obtained in all preterm infants (Fig. 2). The comparison of the metrics obtained in newborns scanned at 1.5T and 3T are reported in the Table 3. Distribution of grey and white matter was different in the subgroups (Table 3). Correlations between the segmented brain MRI structure surfaces with the ASQ score evaluated by adjusted linear regressions are reported in Table 4.

Significant positive correlations with global ASQ score were found for intracranial cavity areas (β = 0.010; P = 0.008), basal ganglia and thalami (β = 0.091; P = 0.0001), gray (β = 0.014; P = 0.043) and white matter surfaces (β = 0.012; P = 0.015), where β represents the correlation between the area and the ASQ score, and P the degree of significance of the correlation. The more parenchyma was present, the better are the ASQ scores. Cerebrospinal fluid and lateral ventricles significantly negatively correlated with global ASQ score (β = −0.021, P = 0.047 and β = −0.088, P = 0.005, respectively). The more cerebrospinal fluid was present; the worse were the ASQ scores. For all ASQ sub-domains (communication abilities, gross motor skills, fine motor skills, problem solving abilities, and

Table 1
Characteristics of very preterm cohort ($n = 390$) and excluded patients ($n = 129$). Comparisons between premature newborns scanned at 1.5T ($n = 338$) and 3T ($n = 52$).

Premature newborns	Analyzed ($n = 390$)	Excluded ($n = 129$)	*P* value	1.5T ($n = 338$)	3T ($n = 52$)	*P*-value
Gestational age (week)	28.57 ± 1.82 [24–33]	28.63 ± 1.70 [26–31]	0.748	28.46 ± 1.77 [24–32]	29.27 ± 1.96 [26–33]	**0.003**
Birth weight (g)	1174 ± 339 [443–2380]	1194 ± 333 [560–1990]	0.554	1158 ± 329 [570–2380]	1258 ± 390 [443–2050]	**0.047**
Birth weight Z score	−0.89 ± 1.54 [−5.23–6.92]	−0.83 ± 1.57 [−4.55–2.44]	0.737	−0.87 ± 1.51 [−5.23–2.76]	−1.01 ± 1.71 [−4.29–6.92]	0.551
Brain growth restriction	133 (133/390; 34.1%)	23 (23/129; 17.8%)	**0.010**	112 (122/338; 33.1%)	21 (21/52; 40.4%)	0.385
Male	227 (227/390; 58.2%)	59 (59/129; 45.7%)	0.125	202 (202/338; 59.8%)	25 (25/52; 48.1%)	0.150
Multiple birth	132 (132/390; 33.8%)	39 (39/129; 30.2%)	0.436	104 (104/338; 30.8%)	28 (28/52; 53.8%)	**0.002**
Antenatal corticosteroids	318 (318/390; 81.5%)	58 (58/129; 44.9%)	0.455	297 (297/338; 87.8%)	21 (21/52; 40.3%)	0.307
Chorioamnionitis	38 (38/390; 9.7%)	7 (7/129; 5.4%)	> 0.999	36 (36/338; 10.6%)	2 (2/52; 3.8%)	0.909
Mean Apgar score at 5 minutes	8.02 ± 1.96 [0–10]	8.05 ± 2.11 [2–10]	0.934	7.99 ± 1.99 [0–10]	8.56 ± 1.29 [5–10]	0.238
Bronchopulmonary dysplasia	74 (74/390; 21.8%)	9 (9/129; 6.9%)	0.053	73 (73/338; 21.6%)	1 (1/52; 1.9%)	**0.001**
Postnatal corticosteroids	28 (28/390; 7.2%)	8 (8/129; 6.2%)	0.923	27 (27/338; 7.99%)	1 (1/52; 1.9%)	0.240
Enterocolitis Bell stage	22 (22/390; 5.6%)	2 (2/129; 1.5%)	0.156	22 (22/338; 6.5%)	0 (0/52; 0.0%)	0.116
Retinopathy stage			0.452			0.113
0	168 (168/390; 43%)	47 (47/129; 36.4%)		150 (150/338; 44%)	18 (18/52; 34.6%)	
1	40 (40/390; 10.2%)	6 (6/129; 10.2%)		40 (40/338; 11.8%)	0 (0/52; 0.0%)	
2	23 (23/390; 9.7%)	4 (4/129; 6.8%)		22 (22/338; 6,5%)	1 (1/52; 1.9%)	
3	5 (5/390; 2.1%)	2 (2/129; 3.4%)		5 (5/338; 1.5%)	0 (0/52; 0.0%)	
Postnatal infection	153 (153/390; 39.2%)	35 (35/129; 27.1%)	0.401	145 (145/338; 42.9%)	8 (8/52; 15.4%)	**0.003**
Transfontanellar ultrasound lesions	69 (69/390; 17.7%)	22 (22/129; 17.1%)	0.975	50 (50/338; 14.8%)	19 (19/52; 36.5%)	**< 0.001**
Transfontanellar ultrasound cavitations	9 (9/390; 2.3%)	3 (3/129; 2.3%)	0.982	9 (9/338; 2.7%)	0 (0/52; 0.0%)	0.487
Transfontanellar ultrasound parenchyma lesions	66 (66/390; 16.9%)	21 (21/129; 16.2%)	0.446	47 (47/338; 13.9%)	19 (19/52; 36.5%)	**< 0.001**
Breast feeding	99 (99/390; 25.3%)	12 (12/129; 9.3%)	0.343	98 (98/338; 29%)	1 (1/52; 1.9%)	0.157
Low educational level	122 (122/390; 31.3%)	26 (26/129; 20.1)	0.738	101 (101/338; 29.8%)	21 (21/52; 40.3%)	**0.033**
Gestational age (wk) at MRI	39.84 ± 1.40 [28–42]	41.10 ± 6.65 [36.43–44.57]	**< 0.001**	39.84 ± 1.30 [30.57–42]	39.82 ± 1.94 [28–41.71]	0.917

Quantitative variables are expressed as means ± standard deviations; numbers in brackets are ranges. Qualitative variables are expressed as raw numbers; numbers in parentheses are proportions followed by percentages. Bold indicates significant *P* value.

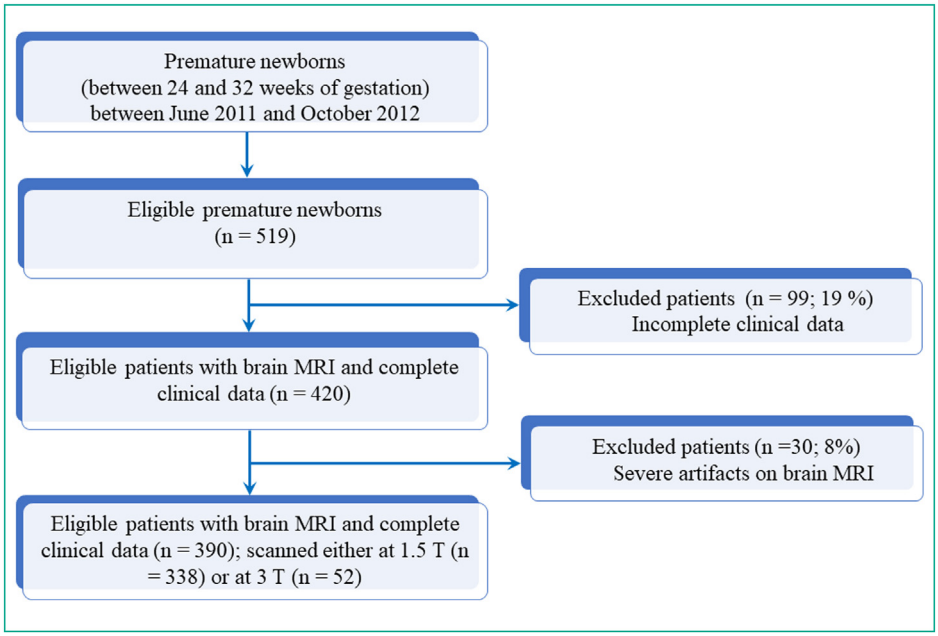

Fig. 1. Flow chart of the included and excluded patient of the EPIRMEX cohort.

Table 2
Mean ASQ sub-domains scores and of the adjusted linear regression coefficients (β) between the basal ganglia and thalami areas with the corresponding ASQ sub-domains.

Age and stage questionnaire domains	Mean score	β	*P*-value
Communication abilities	38.9 ± 17.8 [0–60]	0.02	**0.043**
Gross motor skills	49.1 ± 13.8 [0–60]	0.03	**< 0.001**
Fine motor skills	48.1 ± 10.3 [0–60]	0.02	**< 0.001**
Problem solving abilities	42.3 ± 12.8 [0–60]	0.02	**0.002**
Personal-social skills	43 ± 12.3 [0–60]	0.02	**< 0.001**

ASQ: Age and stage questionnaire variables are expressed as means ± standard deviations; numbers in brackets are ranges. Bold indicates significant *P* value.

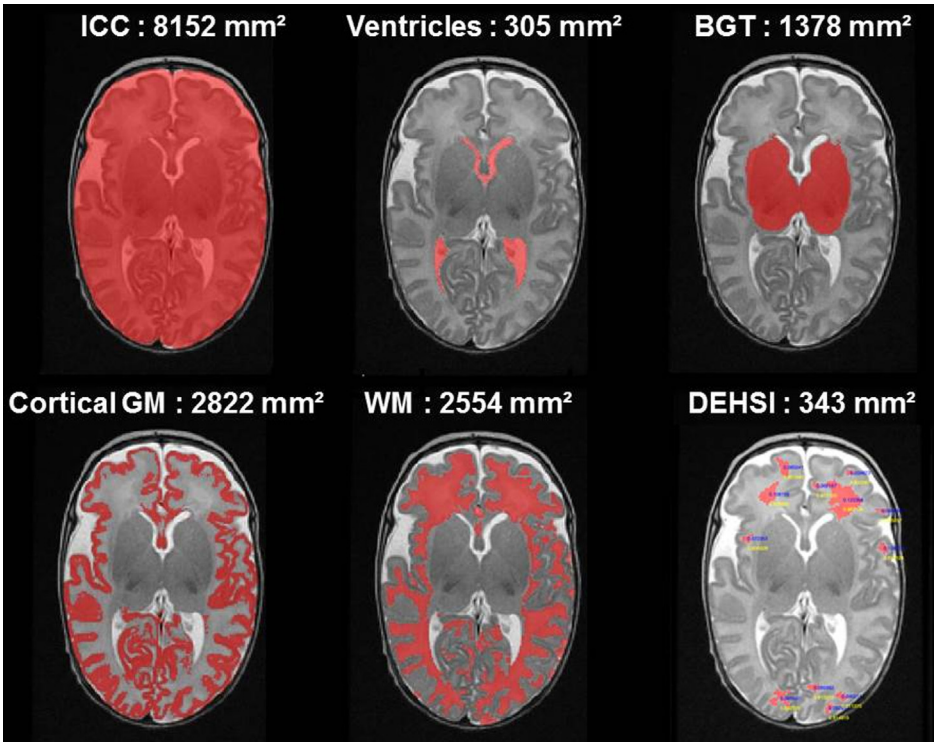

Fig. 2. Segmented turbo spin-echo T2-weighted image in the axial plane from an included premature male, born at 31 weeks of gestation, with a weight of 1860 g. He had a transient hyaline membrane disease. Transfontanellar ultrasound examination showed normal findings. Ventricles metrics were greater than the 75° centile observed in our cohort. Age and stage questionnaire score was 210/300. ICC indicates the intracranial cavity area; BGT indicates basal ganglia and thalami area; GM indicates gray matter; WM indicates white matter; DEHSI indicates diffuse excessive high signal intensity.

personal-social skills), BGT surfaces significantly correlated with the scores (Table 3).

3.3.2. Diffuse excessive high signal intensity

DEHSI was automatically detected in 289 of 390 (74%) included premature newborns with a threshold of 80% of highest intensity of the white matter, 219 (56%) with a threshold of 85% and 144 (37%) with a threshold of 90%. Metrics of DEHSI were higher at 3T, whatever the thresholds. An illustration of the segmentation results with a progressive increase of thresholds (80, 85 and 90%) is provided in Fig. 3. With the highest threshold of 90%, the DEHSI corresponded to the periventricular crossroad areas.

Regardless of the intensity threshold chosen (80%, 85% or 90%) or the magnetic field used, no significant correlation between DEHSI detected by the software and ASQ at 2 years was observed in our cohort (β = −0.003, *P* = 0.664; β = −0.005, *P* = 0.607; β = −0.003, *P* = 0.834). Whisker plots showed mean ASQ score depending on the DEHSI threshold detection (Fig. 4).

4. Discussion

Automated brain metrics provide reliable prognostic information with significant correlation with the neurodevelopmental evolution evaluated with the ASQ score at 2 years of age. Correlations were particularly observed with the surface of BGT; the higher the surface, the better were the neurodevelopmental outcomes. By contrast, the focus on DEHSI did not show any correlation with the ASQ score, regardless of the intensity threshold chosen or the magnetic field, based on our quantitative detection.

Deep gray matter evaluated by the BGT surfaces significantly correlated with the ASQ score and all its sub-domains. Deep grey matter growth rates in preterm newborns are promising biomarkers of long-term outcomes [24,30]. Reduced BGT volumes and slower growth rates in very preterm newborns correlated with distinct neurological dysfunctions at 7 years [31].

Even in our preterm newborns with a “normal” size of lateral ventricles on imaging, the more cerebrospinal fluid was observed, the lower the ASQ score was. Fox et al. also found a relationship between ventricular size at 1 month and outcome in infants less than 30 weeks’ gestation [32]. In this regard, larger lateral ventricles in the parietal region were related to poorer motor development at 2 years, and to slower early language development [32]. Cortical gray matter and white matter surfaces also correlated with the ASQ score. Pittet et. al. have suggested that the brain maturity at term age explored by the radiological aspect of the transient fetal compartments (periventricular crossroad areas, von Monakow segments, subplate compartments) can be assessed on regular T2-weighted MRI [33]. They found a maturity difference in newborn

Table 3
Metrics (in mm^2) obtained in preterm newborns who underwent MRI at 1.5T and at 3T.

	1.5T	3T	*P*-value
Intracranial cavity	7460 ± 768 [2872–9460]	74855 ± 634 [5911–9321]	0.830
Cerebrospinal fluid	860 ± 251 [260–1513]	732 ± 200 [419–1430]	**0.001**
Lateral ventricles	199 ± 86 [79–1079]	163 ± 63 [58–401]	**0.004**
Basal ganglia and thalami	1157 ± 125 [426–1490]	1168 ± 88 [976–1316]	0.559
Gray matter	2512 ± 396 [418–3896]	2206 ± 360 [1223–3268]	**< 0.001**
White matter	2417 ± 468 [922–3954]	3231 ± 356 [2435–4193]	**< 0.001**
DEHSI - threshold > 80 %	255 ± 301 [0–1358]	809 ± 205 [317–1201]	**< 0.001**
DEHSI - threshold > 85 %	123 ± 197 [0–939]	633 ± 234 [71–1047]	**< 0.001**
DEHSI - threshold > 90%	39 ± 98 [0–609]	322 ± 196 [0–663]	**< 0.001**

DEHSI: diffuse excessive high signal intensity. Variables are expressed as means and standard deviations; numbers in brackets are ranges. Bold indicates significant *P* value.

Table 4
Correlation between surfaces of the main brain structures (in mm^2) and ASQ score.

Brain structures	Mean areas (mm^2)	Adjusted β	*P*-value
Intracranial cavity	7475 ± 739 [2873–9473]	0.01	**0.008**
Cerebrospinal fluid	833 ± 257 [168–2048]	−0.02	**0.047**
Lateral ventricles	192 ± 84 [58–1079]	−0.09	**0.005**
Basal ganglia and thalami	1163 ± 120 [426–1490]	0.09	**0.0001**
Gray matter	2469 ± 391 [417–3895]	0.014	**0.043**
White matter	2544 ± 552 [922–4193]	0.012	**0.015**
DEHSI - threshold > 80 %	343 ± 349 [0–1358]	−0.003	0.664
DEHSI - threshold > 85 %	201 ± 273 [0–1140]	−0.005	0.607
DEHSI - threshold > 90 %	79 ± 152 [0–859]	−0.003	0.834

Adjusted β represents the correlation between the area and the ASQ score. ASQ: age and stage questionnaire; DEHSI: diffuse excessive high signal intensity. Variables are expressed as means ± standard deviations; numbers in brackets are ranges. Bold indicates significant *P* value.

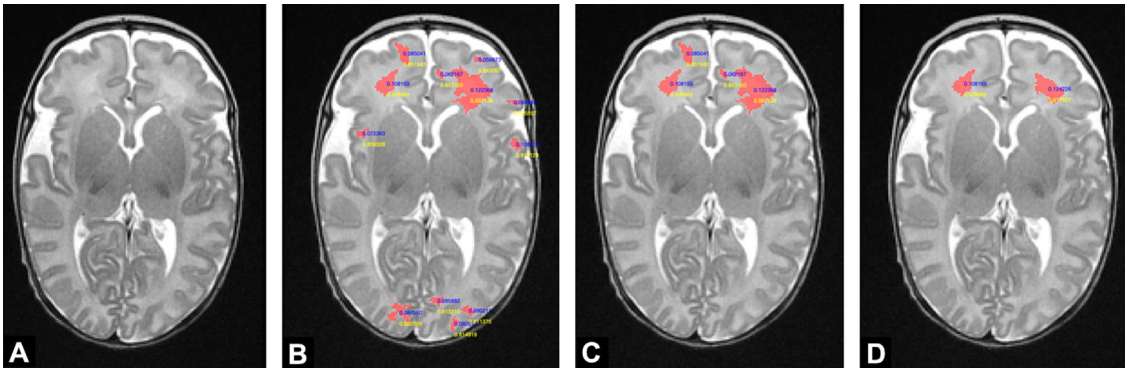

Fig. 3. Turbo spin-echo T2-weighted image in the axial plane. DEHSI segmentation was obtained in the same premature male described in Fig. 1, depending on the chosen threshold: 80% in B, 85% in C, and 90% of maximum intensity signal in D.

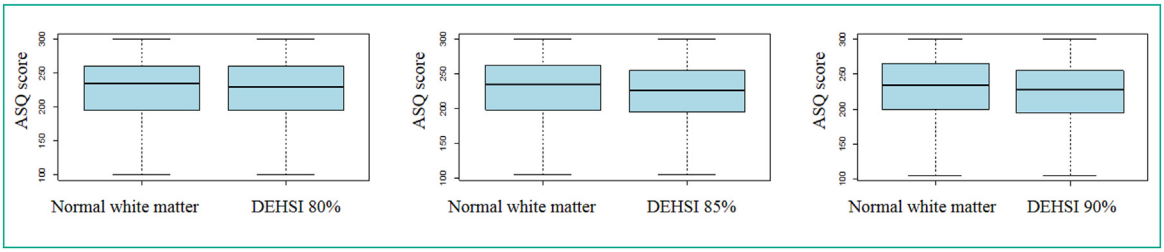

Fig. 4. Whisker plots show mean age and stage questionnaire (ASQ) score depending on the DEHSI threshold detection.

compared to premature newborn at TEA [33], but with the limitation of a subjective visual assessment [34]. Our results suggest that an automated software would be a useful tool to analyze brain MRI more objectively and that it would provide interesting data to predict the neurodevelopmental outcome at two years. While the different thresholds of detection used have influenced the measured DEHSI rates, they had not influenced the lack of correlation observed with the ASQ score. The predictive value of DEHSI did not vary with the intensity threshold. Based on the presented results, without topographical analysis, we hypothesize that the DEHSI might no longer be described as a pathological process with poor prognosis. As all MRI sequence parameters used were homogenized by a medical physicist, no influence of the type of MRI scanner should be expected. However, we did observe an impact of the magnetic field on some particular metrics. Differences in distribution between white and gray matter could be explained by a higher resolution at 3T that would limit the partial volume effect observed at the proximity of the cortical gray matter.

This phenomenon was already described in segmentation review. Another effect of the magnetic field was greater metrics of DEHSI segmented at 3T. It could probably be explained by an increased signal-to-noise ratio and a greater contrast resolution that might have led to a higher sensitivity for revealing DESHI. However, the increased metrics DEHSI did not correlate with a lower ASQ in our cohort. A meta-analysis has recently suggested that DEHSI on TEA-MRI does not predict future development of neurodevelopmental disabilities [35]. This meta-analysis was mainly based on studies that diagnosed DEHSI on visual impression on conventional T2 imaging [35].

Agreed by the American Academy of Pediatrics, the ASQ is a worldwide valid parent completed developmental screening test [28]. ASQ, which is available in France [27], has been presented with arguments to support the cross-cultural validity for other European countries [36]. It allows the parents to be genuinely and centrally involved in the follow-up of their child. Nevertheless, the parents involved in our study may have under- or over-estimated the capabilities of their child. ASQ is a less resource-consuming tool to assess neurodevelopmental outcome but is less sensitive and specific than Bailey III. Potential social and cultural differences between parents are not factors deemed to alter the validity of their neurologic assessment of their child [27]. However, the ASQ questionnaire enabled us to detect more subtle neurological abnormalities by exploring each area of neurologic development.

In the present study, we have segmented one slice per newborn, which was representative of the whole brain, as all main supratentorial brain structures were analyzed, as proposed by Kidokoro et al. [24]. Our metrics results have revealed a correlation between the measured surfaces and the neurodevelopmental evolution, as it was observed in three-dimensional segmentation studies. Our algorithm provides robust metrics results with a processing time less than a minute, without a specific MRI sequence or an experienced user, that could be performed in daily practice. It encourages continuing to use validated automated brain metrics during childhood [37].

A limitation of our study would be a partial exploration of the supratentorial brain stage. Our metrics were a complementary tool to analyze the brain MRI, but a conventional qualitative interpretation of the brain MRI is still required. The evaluation of the volume of the corpus callosum would be of interest but not available in our segmentation algorithm. To analyze neurodevelopmental outcomes further, a detailed segmentation of each specific basal ganglia and the cerebellum evaluation would be necessary. Reproducibility was not evaluated in this study. However, we have obtained good to excellent intra- and inter-observer Dice similarity coefficients while using the algorithm on 1.5T and 3T brain MRI in a previous study [22]. The image quality might influence the Dice similarity coefficients. Indeed, lower quality examinations induced a slightly lower coefficient and a higher variance [38]. As observed in a recent data challenge, although 3D segmentation is useful clinically, the choice of a bi-dimensional segmentation had simplified data collection, annotation, and storage without leading to significant difference of the Dice similarity coefficient among the participants [39]. Another limitation is that the key period for neuropsychometric assessment is around 6 years. As the initial research protocol defined a two-year examination, we have used these data. However, some of the children included in the cohort still have a clinical follow-up. Complementary research studies will be performed on the available long-term follow-up data, despite the possibility of a smaller cohort due to patients lost to follow-up.

In conclusion, in our large prospective, multicentric cohort of preterm newborns, the use of our software revealed a significant correlation between reproducible metrics of the main brain structures with the neurodevelopment at two years of age. Furthermore, the quantitative detection and segmentation of isolated DEHSI of the white matter have allowed excluding any correlation with the neurodevelopment at two years of age. Automated brain MRI metrics are now suitable in daily practice for neonatologists and radiologists.

Human rights

The authors declare that the work described has been carried out in accordance with the Declaration of Helsinki of the World Medical Association revised in 2013 for experiments involving humans.

Informed consent and patient details

The authors declare that this report does not contain any personal information that could lead to the identification of the patient(s).

The authors declare that they obtained a written informed consent from the patients and/or volunteers included in the article. The authors also confirm that the personal details of the patients and/or volunteers have been removed.

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Author contributions

All authors attest that they meet the current International Committee of Medical Journal Editors (ICMJE) criteria for Authorship.

CRediT authorship contribution statement

Guarantors of integrity of entire study, B.M., C.A., C.T., E.S.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; agrees to ensure any questions related to the work are appropriately resolved, all authors; literature research, B.M., P.B., C.T., E.S.; clinical studies, C.G., S.M.; N.K.; statistical analysis, B.M., E.T.; and manuscript editing, all authors.

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Disclosure of interest

The authors declare that they have no competing interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.diii.2020.10.009.

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