Increase in Brain Volumes after Implementation of a Nutrition Regimen in Infants Born Extremely Preterm

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Objective To assess the effect of early life nutrition on structural brain development in 2 cohorts of extremely preterm infants, before and after the implementation of a nutrition regimen containing more protein and lipid.

Study design We included 178 infants retrospectively (median gestational age, 26.6 weeks; IQR, 25.9-27.3), of whom 99 received the old nutrition regimen (cohort A, 2011-2013) and 79 the new nutrition regimen (cohort B, 2013-2015). Intake of protein, lipids, and calories was calculated for the first 28 postnatal days. Brain magnetic resonance imaging (MRI) was performed at 30 weeks postmenstrual age (IQR, 30.3-31.4) and term-equivalent age (IQR, 40.9-41.4). Volumes of 42 (left + right) brain structures were calculated.

Results Mean protein and caloric intake in cohort B (3.4 g/kg per day [$P < .001$] and 109 kcal/kg per day [$P = .038$]) was higher than in cohort A (2.7 g/kg per day; 104 kcal/kg per day). At 30 weeks, 22 regions were significantly larger in cohort B compared with cohort A, whereas at term-equivalent age, only the caudate nucleus was significantly larger in cohort B compared with cohort A.

Conclusions An optimized nutrition protocol in the first 28 days of life is associated with temporarily improved early life brain volumes. *(J Pediatr 2020;223:57-63)*.

In the third trimester of pregnancy, major steps in brain development take place with rapid growth and maturation of important brain structures.[1] Preterm infants are vulnerable to disturbances in cerebral development outside the protecting environment of the womb and previous studies have shown that very preterm infants have smaller brain volumes than healthy full term infants when examined at term-equivalent age (TEA).[2-6] This is important because a decrease in brain volume has been associated with long-term neurodevelopmental consequences, such as behavioral problems and poor cognitive outcomes.[3,7]

Adequate nutrition seems to be crucial for optimal brain growth and maturation; however, it is challenging to provide sufficient amounts of energy and macronutrients enterally during the first weeks in the neonatal intensive care unit (NICU), and parenteral nutrition is often required.[8,9] Recent studies in preterm infants have shown that higher protein and energy intakes in the first months are associated with increased head circumference in the first year and improved cognitive outcomes in childhood and adolescence.[10-14]

Early life nutrition is also important for somatic growth; preterm infants are often significantly underweight at time of hospital discharge and this might have permanent effects in later life.[15-17] Adequate early life nutrition may decrease early postnatal growth restriction and optimize long-term somatic growth and subsequent neurodevelopment in preterm infants.[18]

To date, no studies have examined the effect of macronutrients on neuroimaging-based outcomes in extremely preterm infants with different nutrition regimens. The primary aim of this study was to assess structural brain development in extremely preterm infants who underwent magnetic resonance imaging (MRI) at 30 weeks postmenstrual age (PMA) and again at TEA, before and after the implementation of a new nutrition regimen containing more protein and lipids. We hypothesized that extremely preterm infants who received the new nutrition regimen would show greater brain volumes and increased brain growth between 30 weeks PMA and TEA when compared with infants who received the old regimen. As a secondary aim, differences in somatic growth between the 2 cohorts were examined.

Methods

This retrospective, observational cohort study included infants born from January 2011 to December 2015 with a gestational age of <28 weeks, who were

MRI	Magnetic resonance imaging
NICU	Neonatal intensive care unit
PMA	Postmenstrual age
TEA	Term-equivalent age

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The authors declare no conflicts of interest.

https://doi.org/10.1016/j.jpeds.2020.04.063

admitted to the tertiary NICU of the Wilhelmina Children's Hospital in Utrecht, the Netherlands. Because neuroimaging data were obtained as part of the standard clinical protocol, written informed consent for use of the clinically acquired data was waived by the Institutional Review Board of University Medical Centre Utrecht, the Netherlands.

Clinical data were retrospectively collected from the individual electronical medical records. Z-scores for weight were computed according to the Dutch Perinatal registry references.[19] Small for gestational age was defined as a birth weight of <10th percentile according to curves from Hoftiezer et al.[20] Prolonged mechanical ventilation (defined as >7 days) was used as an indicator for severe illness. Growth was reported as growth velocity as well as z-score change, as recommended by Cormack et al.[21] Growth velocity was calculated by net weight gain over the time interval divided by the weight at the first time point and the number of days.

Infants born before September 2013 received the old nutrition protocol (cohort A), in which parenteral nutrition was introduced on the second day after birth. Protein and lipid intake were slowly increased to a maximum of 2.6 g/kg protein and 1.7 g/kg lipids on the fifth day of life. Infants born in September 2013 or later received the new nutrition protocol (cohort B), which was based on the national guideline developed by the Dutch Society for Paediatrics.[19] In cohort B, parenteral nutrition was started as soon as possible after NICU admission. Protein and lipids were started at 1 g/kg per day on admission and increased to a maximum of 3.5 g/kg protein and 4 g/kg lipids (if serum triglyceride remained <116 mg/dL [3.0 mmol/l]) on the third day. In both protocols, minimal enteral feeding was introduced shortly after birth and enteral intake was increased daily starting at 24-48 hours after birth if tolerated. In cohort A, breast milk was enriched with fortifier, containing additional carbohydrates and proteins, when enteral feeding of 120 mL/kg per day was reached. In cohort B breast milk was enriched when enteral feeding of 100 mL/kg per day was reached. For all patients, total parenteral and enteral protein, lipid, and caloric intake were calculated daily for the first 28 days using the daily prescribed amount of nutritive fluids, assuming 100% bioavailability of enteral nutrients.[21] Kilocalorie content and grams of each macronutrient per 100 mL fluid were sourced from nutritional information printed on parenteral and enteral nutrition products. The energy, protein, and fat concentration per 100 mL of breast milk used to calculate nutrition intake were 68 kcal, 1.0 g, and 4.0 g, respectively. For calculating macronutrients per kilogram, the last known weight was used; infants were weighed every few days. In addition, total days of partial parenteral nutrition were collected.

MRI Protocol

All infants underwent brain MRI at 2 time points: 30 weeks PMA if clinically stable and again around TEA. All infants were scanned on a 3.0 Tesla MR system (Achieva, Philips Medical Systems, Best, the Netherlands). The protocol included T2-weighted imaging in the coronal plane (30 weeks PMA: repetition time 10 085 ms, echo time 120 ms, slice thickness 2 mm; and TEA: repetition time 4847 ms, echo time 150 ms, slice thickness 1.2 mm). At 30 weeks PMA, infants were scanned in an MRI-compatible incubator with a neonatal head coil (Dräger MR incubator, Lübeck, Germany, or Nomag IC 3.0, Lammers Medical Technology GmbH, Lübeck, Germany) and at TEA, a SENSE head coil was used. During the examination a neonatologist or physician assistant was present, and oxygen saturation, respiratory rate, and heart rate were monitored. If necessary, infants were sedated using oral chloral hydrate (30 mg/kg at 30 weeks PMA and 50-60 mg/kg at TEA). All infants received hearing protection using Minimuffs (Natus Medical Incorporated, San Carlos, California) and Earmuffs (EM's 4 Kids, Brisbane, Australia). Intraventricular hemorrhage was graded according to Papile and post-hemorrhagic ventricular dilatation was defined as a ventricular index of >97th percentile.[22,23] Severe brain injury was defined as grade 3 or 4 intraventricular hemorrhage, post-hemorrhagic ventricular dilatation requiring drainage, cystic periventricular leukomalacia, or a large cerebellar hemorrhage (involving >50% of 1 hemisphere).

The obtained T2-weighted images were segmented into different tissue classes using an automatic segmentation method (**Figure 1**; available at www.jpeds.com).[24] This technique is highly accurate across a wide range of PMA, from 24 weeks to TEA. Scans were checked for quality and scans with severe movement artifacts were excluded. Minor manual editing took place if necessary. Volumes of all tissue regions were computed and corrected for PMA at time of scan. If good quality segmentation was available at both 30 weeks PMA and TEA (serial MRI), absolute and relative brain growth were calculated between 30 weeks PMA and TEA. Absolute brain growth was calculated by subtracting volumes at 30 weeks PMA from volumes at TEA. Relative brain growth was calculated dividing volumes at TEA by volumes at 30 weeks PMA, resulting in a number showing the increase in (regional) brain size at TEA compared with 30 weeks PMA.

Statistical Analyses

Statistical analysis was performed using R version 3.5.2 (The R Foundation, Vienna, Austria). Depending on distribution of the data, Student t tests or Mann-Whitney U tests (continuous data) and χ^2 statistics (categorical data) were performed to analyze differences in baseline characteristics and nutritional data between cohorts A and B. Brain volumes were corrected for PMA at time of scan. Brain volumes were compared between cohorts A and B using univariable linear regression analysis. Mixed effect modelling was used to determine whether brain growth between 30 weeks PMA and TEA was different between both cohorts. Somatic growth was compared between cohorts A and B using an independent t test. A P value of <.05 was considered significant.

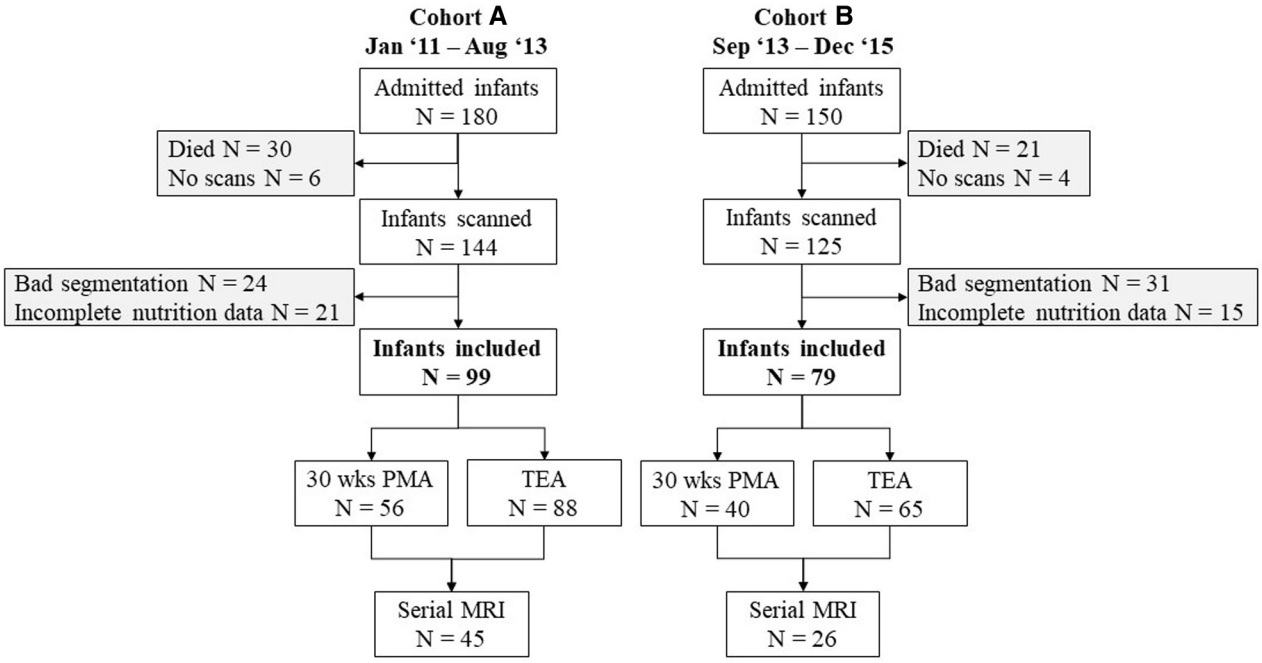

Figure 2. Flowchart patient inclusion. Infants with no scans in cohort A (n = 6) were all unstable at 30 weeks PMA and at TEA. Parents of 2 infants refused the scan and 4 infants had other reasons than being unstable or refusing parents for no scan, including logistic reasons; 144 infants were scanned at least once. Infants with no scans in cohort B (n = 4) did not have a scan because parents refused (n = 1) or for other reasons than being unstable or refusing parents, including logistic reasons (n = 3); 125 infants were scanned at least once.

Results

During the study period, 330 infants born at <28 weeks of gestation were admitted to the NICU. Fifty-one infants died and 37 did not undergo MRI (**Figure 2**). Infants were included in this study if segmentation and nutrition measures were available, resulting in 99 infants in cohort A and 79 infants in cohort B. Serial MRI was available for 45 infants in cohort A and 26 infants in cohort B. Infants who were included in this study were less often diagnosed with severe brain injury (10%) than were excluded infants (26%; $P < .001$) (**Table I**; available at www.jpeds.com). No significant differences were seen in baseline characteristics between infants in cohort A and cohort B (**Table II**). Infants in cohort B had significantly higher daily protein (3.4 g/day vs 2.7 g/day, +23%; $P < .001$) and caloric (109 kcal/day vs 104 kcal/day, +3.5%; $P = .038$) intakes in the first 28 days compared with infants in cohort A (**Table III**).

At 30 weeks PMA, total brain volume and grey matter were significantly greater in cohort B compared with cohort A (**Table IV**; available at www.jpeds.com). This was also demonstrated in significantly larger volumes in 14 of 16 regional grey matter volumes (**Figure 3**) and (**Table IV** [available at www.jpeds.com]). White matter volume was comparable between cohort A and B, although 1 of 16 white matter regions was significantly larger in cohort B. Seven subcortical regions, including the cerebellum, were significantly larger in cohort B.

At TEA, no differences were seen in total brain volume, grey matter volume, and white matter volume. The caudate nucleus was the only region significantly larger in cohort B compared with cohort A. Greater total brain volumes and grey matter volumes at 30 weeks PMA and greater caudate nucleate volumes at TEA in cohort B remained significant

Table II. Baseline characteristics of the included infants

Characteristics	Cohort A (n = 99)	Cohort B (n = 79)	*P* value
Male	45 (46)	39 (49)	.71
Gestational age, wk	26.4 [25.7-27.3]	26.6 (25.9-27.2)	.76
Birth weight, g	865 [750-998]	875 (720-1000)	.87
Birth weight z-score	0.31 ± 0.90	0.23 ± 0.91	.56
Small for gestational age (<10th percentile)	21 (21)	21 (27)	.51
Multiplicity	29 (29)	22 (28)	.91
Apgar at 5 minutes	8 [7-9]	8 [6-8]	.04*
Days parental nutrition	12 [9-16]	13 [10-18]	.24
>7 d of ventilation	50 (51)	40 (51)	1.00
Abdominal surgery	9 (9.1)	6 (7.6)	.93
Severe brain injury	10 (10)	8 (10)	1.00
Postnatal hydrocortisone	32 (32)	17 (22)	.13
Sepsis	41 (41)	30 (38)	.76

Values are median [IQR], mean ± SD, or number (%).
Continuous data were tested using a Student *t* test or Mann-Whitney *U* test, depending on the distribution of the data, categorical data was tested using χ^2 statistics.
Small for gestational age is defined as a birth weight of <10th percentile.[20] Severe brain injury was defined as intraventricular hemorrhage grade 3 or 4, post-hemorrhagic ventricular dilatation requiring drainage, cystic periventricular leukomalacia or a large cerebellar hemorrhage (involving >50% of 1 hemisphere).
*Significant differences between cohort A and B at an .05 level.

Table III. Comparison of cumulative intake

	Cohort A (n = 99)		Cohort B (n = 79)		
Nutrients	28 days	Daily	28 days	Daily	*P* value
Protein, g/kg	75 [71-82]	2.7 [2.5-2.9]	97 [93-99]	3.5 [3.3-3.5]	<.001
Lipids, g/kg	135 [121-148]	4.8 [4.3-5.3]	134 [122-144]	4.8 [4.4-5.1]	.57
Calories, kcal/kg	2924 [2707-3149]	104 [97-112]	3045 [2866-3177]	109 [102-113]	.038

Daily intake means average daily intake, calculated by dividing total intake over 28 days by 28. Numbers are presented as median [IQR].

in sensitivity analyses that excluded infants with severe brain injury or abdominal surgery.

Figure 4 (available at www.jpeds.com) shows relative growth of all brain regions between 30 weeks PMA and TEA in a subgroup of infants from both cohorts with MRI at both time points (n = 71; Figure 4). White matter structures were on average 1.7 times larger at TEA compared with 30 weeks PMA, whereas grey matter structures were approximately 3.6 times larger. Of the subcortical structures, the cerebellum had the most rapid increase and was 3.8 times larger at TEA compared with 30 weeks PMA. No differences were seen between the cohorts in brain growth from 30 weeks PMA to TEA in total brain volume and overall grey and white matter volume, although 1 grey matter region showed significantly increased growth in cohort A compared with cohort B (the cingulate gyrus, anterior part; $P = .012$).

Infants in cohort B showed increased relative somatic growth compared with infants in cohort A between birth and 30 weeks PMA (13.1 g/kg/day vs 10.0 g/kg/day; $P < .001$). Infants in cohort B also had significantly less decrease in weight z-score between birth and 30 weeks PMA (−0.61 vs −0.88; $P = .002$) and between birth and TEA (−0.90 vs −1.21; $P = .036$).

Discussion

This study examined the effect of greater nutrient intakes in the first 28 days of life on brain volumes and somatic

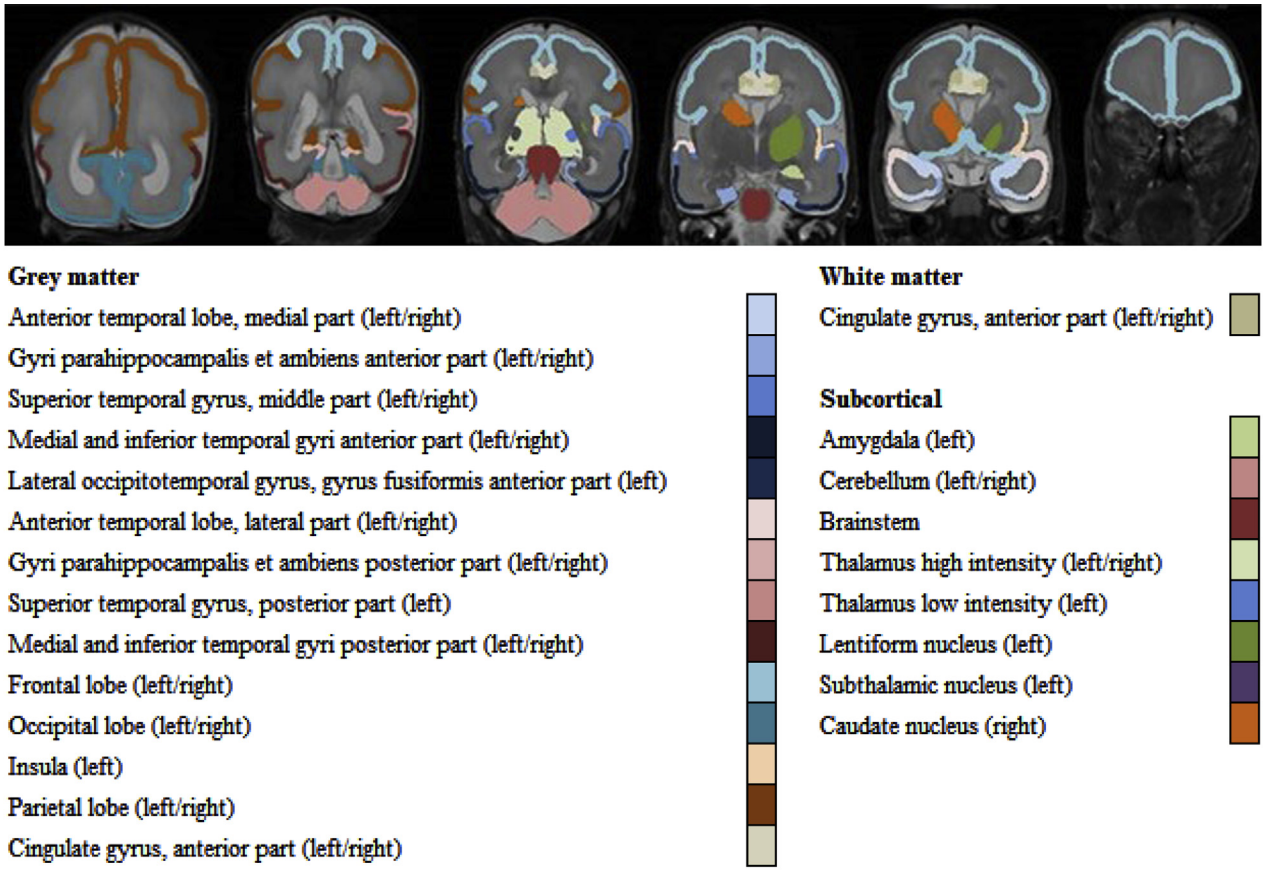

Figure 3. This figure shows all brain regions that are significantly larger in cohort B than in cohort A at 30 weeks PMA.

growth, measured at 30 weeks PMA and TEA in extremely preterm infants. At 30 weeks PMA, infants who received the enriched nutrition regimen showed significantly larger brain volumes. At TEA, the right caudate nucleus was the only region significantly larger in cohort B compared with cohort A. Infants in the enriched nutrition cohort had improved weight gain and less of a decline in weight z-score between birth and 30 weeks PMA and between birth and TEA.

Greater brain volumes were most evident at 30 weeks PMA in the cohort of extremely preterm infants receiving an enriched nutrition regimen in the first 28 days. This finding is consistent with a recent published study that showed total protein, lipid, and energy intake to be positively associated with total cerebral volume at 30 weeks PMA and TEA.[25] The results of our study suggest a beneficial effect of increased nutrient intake in the first weeks after birth for optimized brain volumes in extremely preterm born infants.

We found that cortical grey matter and subcortical structures grew faster than white matter regions between 30 weeks PMA and TEA, consistent with the few studies published to date regarding serial MRI.[1,6] It is known that substantial brain growth occurs during the third trimester, especially in the cortical grey matter volume.[26,27] In this study at 30 weeks PMA, greater volumes in the enriched nutrition cohort were more frequently seen in cortical grey matter and subcortical regions than in white matter regions. The findings of our study might suggest that brain regions with the highest growth rate in the third trimester of gestation are more vulnerable to nutritional deficits in early preterm life.

In this study, the right caudate nucleus, a very vulnerable structure in preterm infants, was the single brain structure that was significantly larger at TEA in the cohort with the enriched nutrition protocol. A previous study also demonstrated greater caudate volumes in preterm-born adolescents after an enriched postnatal diet containing more protein and calories.[7] Our study suggests that the caudate nucleus is a structure that might benefit from enriched nutrition. This finding is of clinical relevance, because previous studies showed decreased caudate nucleus volumes correlated with lower IQs, hyperactivity, and reduced working memory in children born prematurely.[28-30] In contrast, a doubling of the growth rate in the caudate nucleus at later ages has been described in individuals with autism compared with control subjects, indicating that growth rate might be of more interest than volume per se.[31] Our study found asymmetry of the caudate nucleus volume, because only the right caudate nucleus was significantly larger in cohort B. Asymmetry with a greater right relative to left caudate volume has previously been associated with attentional problems, indicating that our finding might be of clinical relevance.[32,33]

Despite there being no significant differences in brain growth from 30 weeks PMA to TEA between the cohorts, differences in brain volumes mostly disappeared at TEA. However, nutrition details were only collected for the first 28 days after birth. Similarly, a recently published study did not show associations between nutritional intake in the first 28 days and brain volumes at TEA.[34] After 30 weeks PMA, non-nutritional factors such as surgery or lung disease, might influence volumetric brain growth.[35] Future studies should evaluate the effect of nutritional intake after the first weeks and should assess quality of this catch-up growth.

Infants from our cohorts were still underweight at TEA. This phenomenon has previously been described as a major problem in preterm and very low birth weight infants.[15,36] We also found that infants' z-scores decreased from birth until TEA, raising the concern that subnormal somatic growth may persist during childhood or later in life, as has been described in previous studies.[37-39] However, we found improved weight gain and a lesser decline in weight z-score between birth and 30 weeks PMA in the cohort that received higher protein and caloric intake. Previous studies also have shown improved somatic growth after optimized nutritional intake.[34,40] Somatic growth from birth to discharge has been associated with long-term motor development in previous studies, so improving neonatal growth with adequate nutrition might be crucial for improved long-term outcome in extremely preterm infants.[18,41]

The strengths of this study include the extended time of inclusion over a period of five years, which allowed detailed comparison of 2 nutrition regimens. This study was a first step toward understanding the potential vulnerability of specific brain tissues to inadequate nutrition in early life in extremely preterm infants. Future studies including neuroimaging-based outcomes and long-term neurodevelopmental follow-up are warranted to elucidate the clinical impact of improved nutrition on neurodevelopmental outcome in preterm infants.

This study has several limitations. Differences in brain size may be explained by factors other than the change in nutrition practice. We did not observe differences between the cohorts in rates of clinical conditions or treatment variables (**Table II**). Furthermore, no major changes in protocols occurred during the inclusion period. Nevertheless, the potential of unmeasured confounding variables needs to be acknowledged. Second, this cohort was relatively healthy, because MRI at 30 weeks could only be performed in infants who were sufficiently stable. A proportion of scans at 30 weeks PMA had to be excluded for automated segmentation owing to severe movement artifacts of the T2 weighted scan. As seen in **Table I**, infants with severe brain injury were more often excluded compared with infants without severe brain injury, owing to less adequate automatic segmentation. The conclusions of this study might therefore be less relevant to preterm infants with severe brain injury. It should also be noted that, at 30 weeks PMA, the sickest infants could not be scanned and were therefore only included at TEA. Third, although the new nutrition protocol in our study prescribed a higher amount of lipids compared with the old nutrition protocol, lipid intake did not differ between cohorts. Therefore, no conclusions can be drawn concerning the influence of lipid intake on brain volumes. Furthermore, our evaluation of neonatal growth and nutrition differed in some ways from

published recommendations.[21] In future studies, weight velocity should be calculated using the exponential method to provide the best accuracy, and standardized (preterm) breast milk composition should be used when calculating nutrient intake.[42] Finally, the problem of multiple testing might have occurred comparing multiple brain structures. In our opinion, applying Bonferroni correction would have been far too conservative with regard to our research question and hypothesis. Although the single larger white matter structure at 30 weeks PMA might indeed have been significant owing to chance, the significantly greater grey matter volumes seen in almost all grey matter regions were convincing for increased grey matter volumes in cohort B.

We found that an optimized nutrition protocol that included higher protein and caloric intakes in the first 28 days was associated with greater early life brain volumes and improved somatic growth in extremely preterm infants. Because this study showed potential benefits of adequate nutrition, it is highly recommended to optimize nutrition protocols in daily clinical practice. ■

Submitted for publication Nov 8, 2019; last revision received Apr 2, 2020; accepted Apr 24, 2020.

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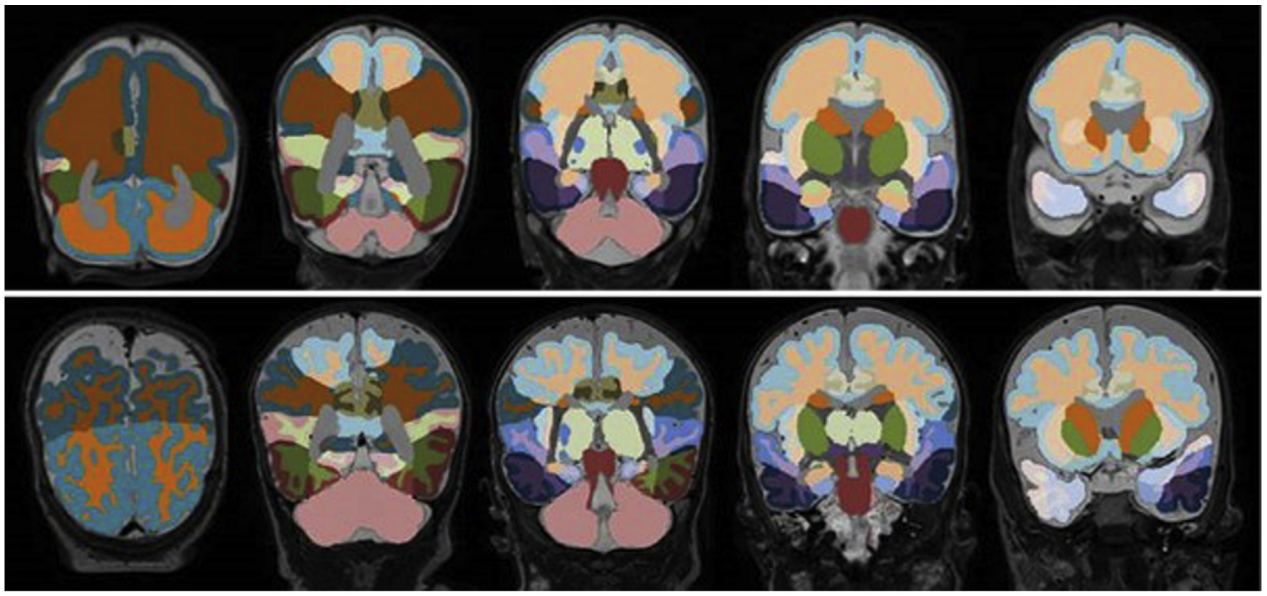

Grey matter and white matter regions	GM	WM	Subcortical regions
Anterior temporal lobe, medial part (left/right)			Hippocampus (left/right)
Gyri parahippocampalis et ambiens anterior part (left/right)			Amygdala (left/right)
Superior temporal gyrus, middle part (left/right)			Cerebellum (left/right)
Medial and inferior temporal gyri anterior part (left/right)			Brainstem
Lateral occipitotemporal gyrus, gyrus fusiformis anterior part (left/right)			Caudate nucleus (left/right)
Anterior temporal lobe, lateral part (left/right)			Thalamus high intensity (left/right)
Gyri parahippocampalis et ambiens posterior part (left/right)			Thalamus low intensity (left/right)
Superior temporal gyrus, posterior part (left/right)			Lentiform nucleus (left/right)
Lateral occipitotemporal gyrus, gyrus fusiformis posterior part (left/right)			Subthalamic nucleus (left/right)
Medial and inferior temporal gyri posterior part (left/right)			Lateral ventricle (left/right)
Insula (left/right)			Corpus callosum
Frontal lobe (left/right)			
Occipital lobe (left/right)			
Parietal lobe (left/right)			
Cingulate gyrus, anterior part (left/right)			
Cingulate gyrus, posterior part (left/right)			

Figure 1. Segmented brain regions at 30 weeks PMA (*top*) and TEA (*bottom*) using the automatic segmentation method from Makropoulos et al 2014.[25] The obtained T2-weighted images were segmented into 84 different tissue classes using an automatic segmentation method.[34] This technique is highly accurate across a wide range of PMAs, from 24 weeks gestational age to TEA. *GM*, grey matter; *WM*, white matter.

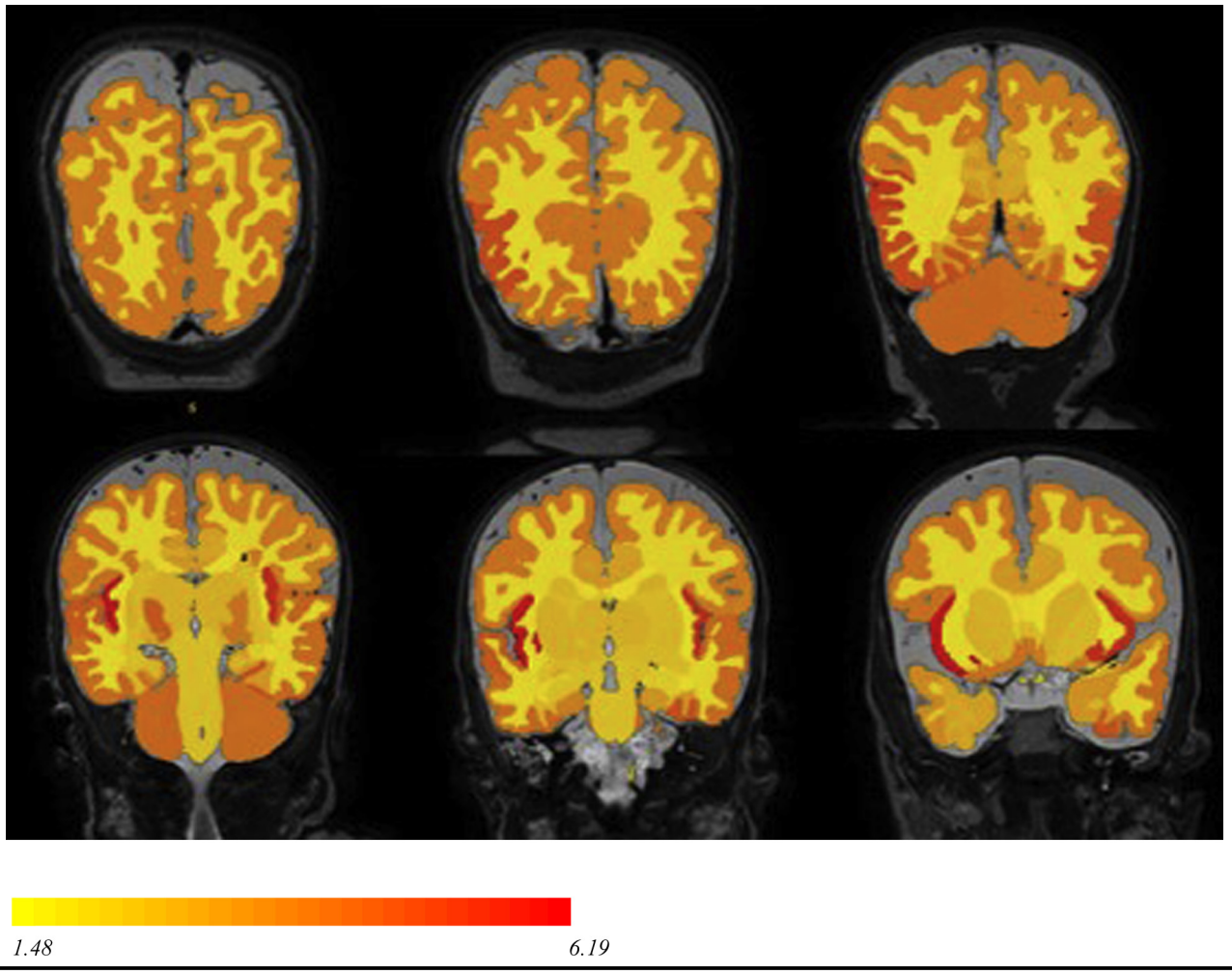

Figure 4. Relative brain growth of all brain regions between 30 weeks PMA and TEA for all infants with serial MRI. A spectrum from light yellow to dark red represents respectively the least rapid up to the most rapid growth. The region with the least rapid growth (left white matter insula) was 1.48 times larger at TEA compared with 30 weeks PMA, region with the most rapid growth (right grey matter insula) was 6.19 times larger at TEA compared with 30 weeks PMA.

Table I. Baseline characteristics of all infants

Characteristics	Included infants (n = 176)	Excluded infants (n = 152)	*P* value
Male	84 (47)	81 (53)	.27
Gestational age, wk	26.6 (25.9, 27.3)	26.3 (25.1, 27.3)	.11
Birth weight, g	870 (743, 1000)	800 (696, 1000)	.076
Birth weight z-score	0.28 (−0.28, 0.85)	0.18 (−0.38, 0.75)	.30
Days parental nutrition	13 (10, 17)	12 (9, 20)	.73
>7 d of ventilation	91 (51)	85 (56)	.38
Abdominal surgery	15 (8.4)	23 (15)	.057
Severe brain injury	18 (10)	39 (26)	<.001

Values are presented as median (Q1, Q3) or number (%).

Table IV. Brain volumes

Regions	30 Weeks PMA				TEA			
	Cohort A (n = 56)	Cohort B (n = 40)	Mean difference (95% CI)	*P* value	Cohort A (n = 88)	Cohort B (n = 65)	Mean difference (95% CI)	*P* value
Grey matter	44 319 ± 6275	48 298 ± 6722	3980 (1323 to 6637)	.004*	158 665 ± 17 499	159 126 ± 18 394	461 (−5318 to 6240)	.875
Anterior temporal lobe, medial part	666 ± 118	723 ± 121	57 (8 to 106)	.023*	1819 ± 268	1833 ± 314	13 (−80 to 107)	.778
Anterior temporal lobe, lateral part	576 ± 98	627 ± 91	51 (12 to 90)	.011*	1809 ± 317	1860 ± 357	52 (−56 to 160)	.346
Gyri parahippocampalis et ambiens anterior part	706 ± 176	804 ± 183	98 (24 to 171)	.010*	2100 ± 298	2137 ± 285	37 (−57 to 132)	.439
Superior temporal gyrus, middle part	1315 ± 242	1502 ± 289	187 (79 to 295)	.001*	5252 ± 726	5415 ± 754	162 (−76 to 401)	.180
Medial and inferior temporal gyri anterior part	1246 ± 198	1398 ± 187	153 (73 to 232)	<.001*	4811 ± 621	4848 ± 600	37 (−161 to 235)	.713
Lateral occipitotemporal gyrus, gyrus fusiformis anterior part	382 ± 73	418 ± 93	36 (2 to 69)	.039*	1518 ± 197	1550 ± 221	32 (−35 to 99)	.345
Insula	761 ± 168	831 ± 169	70 (0 to 139)	.049*	4269 ± 693	4164 ± 693	−104 (−328 to 120)	.360
Occipital lobe	6969 ± 887	7577 ± 1139	608 (198 to 1019)	.004*	24 969 ± 3217	25 274 ± 3432	305 (−765 to 1374)	.574
Gyri parahippocampalis et ambiens posterior part	385 ± 87	441 ± 83	56 (21 to 91)	.002*	1495 ± 225	1467 ± 215	−28 (−99 to 44)	.443
Lateral occipitotemporal gyrus, gyrus fusiformis posterior part	476 ± 107	500 ± 101	24 (−19 to 67)	.269	1936 ± 295	1928 ± 271	−9 (−101 to 84)	.854
Medial and inferior temporal gyri posterior part	1864 ± 310	2070 ± 340	206 (74 to 339)	.003*	8558 ± 1134	8476 ± 1072	−82 (−440 to 276)	.652
Superior temporal gyrus, posterior part	634 ± 132	707 ± 161	72 (13 to 132)	.018*	2800 ± 429	2826 ± 415	26 (−110 to 163)	.703
Cingulate gyrus, anterior part	1336 ± 282	1500 ± 292	164 (46 to 282)	.007*	3711 ± 654	3540 ± 609	−171 (−377 to 34)	.101
Cingulate gyrus, posterior part	1443 ± 317	1490 ± 316	48 (−83 to 178)	.470	3824 ± 578	3714 ± 543	−110 (−292 to 72)	.236
Frontal lobe	14 814 ± 2226	16 049 ± 2134	1235 (336 to 2135)	.008*	52 248 ± 6370	52 410 ± 6896	161 (−1971 to 2293)	.881
Parietal lobe	10 745 ± 1721	11 660 ± 1918	914 (172 to 1657)	.016*	37 547 ± 4194	37 685 ± 4189	1092 (−3644 to 5828)	.841
White matter	73 915 ± 9920	76 818 ± 8452	2902 (−937 to 6741)	.137	126 374 ± 14 577	127 466 ± 14 761	138 (−1217 to 1493)	.649
Anterior temporal lobe, medial part	300 ± 69	314 ± 81	14 (−17 to 45)	.363	791 ± 147	813 ± 178	22 (−29 to 74)	.395
Anterior temporal lobe, lateral part	395 ± 83	419 ± 80	24 (−10 to 57)	.164	771 ± 132	812 ± 159	41 (−6 to 87)	.085
Gyri parahippocampalis et ambiens anterior part	344 ± 85	352 ± 128	7 (−36 to 51)	.732	690 ± 167	730 ± 174	40 (−15 to 95)	.155
Superior temporal gyrus, middle part	2619 ± 378	2760 ± 408	140 (−20 to 301)	.086	4228 ± 469	4322 ± 599	94 (−76 to 265)	.277
Medial and inferior temporal gyri anterior part	3090 ± 505	3216 ± 353	126 (−58 to 311)	.176	5076 ± 693	5148 ± 549	73 (−133 to 278)	.485
Lateral occipitotemporal gyrus, gyrus fusiformis anterior part	609 ± 111	621 ± 155	12 (−41 to 66)	.648	1485 ± 223	1510 ± 274	25 (−54 to 105)	.529
Insula	2683 ± 417	2838 ± 438	155 (−20 to 330)	.082	4040 ± 603	4195 ± 665	154 (−49 to 358)	.136
Occipital lobe	8873 ± 1190	9247 ± 1221	374 (−120 to 869)	.136	14 222 ± 2247	14 570 ± 2296	348 (−385 to 1081)	.350
Gyri parahippocampalis et ambiens posterior part	438 ± 92	441 ± 78	3 (−33 to 38)	.889	969 ± 161	970 ± 138	0 (−48 to 49)	.985
Lateral occipitotemporal gyrus, gyrus fusiformis posterior part	692 ± 122	710 ± 123	18 (−33 to 68)	.489	2023 ± 314	2025 ± 351	2 (−105 to 108)	.977
Medial and inferior temporal gyri posterior part	4383 ± 628	4478 ± 563	95 (−153 to 342)	.449	7170 ± 1064	7213 ± 894	43 (−279 to 364)	.793
Superior temporal gyrus, posterior part	1442 ± 223	1512 ± 268	70 (−30 to 170)	.167	2330 ± 375	2347 ± 398	17 (−107 to 141)	.788
Cingulate gyrus, anterior part	864 ± 192	972 ± 206	108 (27 to 189)	.010*	2325 ± 349	2366 ± 381	41 (−77 to 158)	.494
Cingulate gyrus, posterior part	931 ± 205	985 ± 195	54 (−29 to 137)	.198	2210 ± 282	2293 ± 330	82 (−16 to 181)	.098
Frontal lobe	29 110 ± 4187	30 498 ± 3780	1388 (−266 to 3042)	.099	49 087 ± 5916	49 088 ± 5709	1 (−1883 to 1885)	.999
Parietal lobe	17 142 ± 2759	17 456 ± 2145	314 (−723 to 1351)	.549	28 957 ± 3988	29 065 ± 3959	108 (−1176 to 1393)	.868

(*continued*)

Table IV. Continued

Regions	30 Weeks PMA				TEA			
	Cohort A (n = 56)	Cohort B (n = 40)	Mean difference (95% CI)	*P* value	Cohort A (n = 88)	Cohort B (n = 65)	Mean difference (95% CI)	*P* value
Subcortical regions								
Hippocampus	710 ± 92	743 ± 85	34 (−3 to 70)	.072	1352 ± 143	1367 ± 159	15 (−33 to 64)	.535
Amygdala	390 ± 65	428 ± 58	38 (13 to 64)	.004*	887 ± 99	911 ± 94	24 (−7 to 55)	.130
Cerebellum	6279 ± 1077	6851 ± 1119	572 (122 to 1022)	.013*	23 839 ± 3106	24 167 ± 3295	327 (−703 to 1357)	.531
Brainstem	2720 ± 270	2924 ± 332	204 (82 to 326)	.001*	5510 ± 496	5619 ± 519	109 (−55 to 272)	.191
Caudate nucleus	1552 ± 208	1604 ± 223	52 (−36 to 140)	.245	3507 ± 391	3658 ± 428	152 (20 to 283)	.024*
Thalamus high intensity	3143 ± 400	3356 ± 402	213 (49 to 378)	.012*	7374 ± 639	7477 ± 696	103 (−111 to 317)	.344
Thalamus low intensity	284 ± 65	324 ± 61	41 (15 to 67)	.003*	1052 ± 153	1034 ± 123	−18 (−64 to 27)	.430
Subthalamic nucleus	213 ± 40	231 ± 33	17 (2 to 32)	.028*	457 ± 44	467 ± 49	10 (−5 to 25)	.200
Lentiform nucleus	2606 ± 365	2772 ± 413	165 (7 to 324)	.041*	5767 ± 688	5900 ± 719	133 (−94 to 359)	.249
Corpus callosum	783 ± 140	827 ± 170	44 (−19 to 107)	.165	2170 ± 303	2168 ± 306	−2 (−100 to 97)	.975
Lateral ventricle	6001 ± 1914	6239 ± 2397	237 (−637 to 1112)	.591	10 310 ± 3678	10 389 ± 6094	80 (−1488 to 1647)	.920
Total brain volume	142 914 ± 16 666	151 415 ± 16 380	8500 (1698 to 15 302)	.015*	347 264 ± 33 698	349 749 ± 34 298	2485 (−8487 to 13 457)	.655

Volumes are presented in mm^3 as mean ± SD. Total brain volume is the sum of all regional volumes presented above. Differences in means between cohorts A and B are presented as mean difference (95% CI).
*Significant differences between cohort A and B that were significant on a .05 level.