Title

Early Lipid Intake Improves Cerebellar Growth in Very Low-Birth-Weight Preterm Infants

Journal

Journal of Parenteral and Enteral Nutrition, 45(3)

ISSN

0148-6071

Authors

Ottolini, Katherine M

Andescavage, Nickie

Kapse, Kushal

et al.

Publication Date

2021-03-01

DOI

10.1002/jpen.1868

Peer reviewed

HHS Public Access

Author manuscript

JPEN J Parenter Enteral Nutr. Author manuscript; available in PMC 2021 October 07.

Published in final edited form as:

JPEN J Parenter Enteral Nutr. 2021 March ; 45(3): 587–595. doi:10.1002/jpen.1868.

Early Lipid Intake Improves Cerebellar Growth in Very Low-Birth-Weight Preterm Infants

Katherine M. Ottolini, MD[1,2], **Nickie Andescavage, MD**[3,7], **Kushal Kapse, MS**[4], **Marni Jacobs, PhD, MPH**[5], **Jonathan Murnick, MD**[6], **Rebecca VanderVeer, LD**[3], **Sudeepta Basu, MD**[3,7], **Mariam Said, MD**[3,7], **Catherine Limperopoulos, PhD**[4,8]

[1]Department of Neonatology, 18th Medical Operations Squadron, Kadena AB, Okinawa, Japan;

[2]Department of Pediatrics, Division of Neonatology, Uniformed Services University, Bethesda, Maryland, USA;

[3]Department of Neonatology, Children's National Hospital, Washington, District of Columbia, USA;

[4]Developing Brain Research Laboratory, Children's National Hospital, Washington, District of Columbia, USA;

[5]Division of Biostatistics & Study MethodologyChildren's National Hospital, Washington, District of Columbia, USA;

[6]Department of Radiology, Children's National Hospital, Washington, District of Columbia, USA;

[7]Department of Pediatrics, George Washington University School of Medicine, Washington, District of Columbia, USA;

[8]Department of Radiology, George Washington University School of Medicine, Washington, District of Columbia, USA.

Abstract

Background: Despite recent advances in nutrition practice in the neonatal intensive care unit, infants remain at high risk for growth restriction following preterm birth. Additionally, optimal values for macronutrient administration, especially lipid intake, have yet to be established for preterm infants in the extrauterine environment.

Methods: We studied preterm infants born at very low-birth weight (VLBW, <1500 g) and ≤32 weeks' gestation. Cumulative macronutrient (carbohydrate, lipid, protein, energy) intake in the first 2 and 4 weeks of life was compared with total and regional brain volumes on magnetic

Corresponding Author: Catherine Limperopoulos, PhD, Center for the Developing Brain, Diagnostic Imaging and Radiology, 111 Michigan Ave NW, Washington, DC 20010, USA. climpero@childrensnational.org.

Statement of Authorship

C. Limperopoulos, N. Andescavage, and K. Ottolini equally contributed to the conception and design of the research; K. Ottolini and N. Andescavage contributed to the design of the research; K. Ottolini, K. Kushal, M. Jacobs, J. Murnick, R. VanderVeer, S. Basu, and M. Said contributed to the acquisition and analysis of the data; K. Ottolini, M. Jacobs, and N. Andescavage contributed to the interpretation of the data; and K. Ottolini drafted the manuscript. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

Conflicts of interest: None declared.

resonance imaging (MRI) obtained at term-equivalent age. Preterm infants had no structural brain injury on conventional MRI.

Results: In a cohort of 67 VLBW infants, cumulative lipid intake in the first 2 weeks of life was positively associated with significantly greater cerebellar volume ($\beta = 95.8$; $P = .01$) after adjusting for weight gain, gestational age at birth, and postmenstrual age at MRI. Cumulative lipid ($\beta = 36.1$, $P = .01$) and energy ($\beta = 3.1$; $P = .02$) intake in the first 4 weeks of life were both significantly associated with greater cerebellar volume. No relationship was seen between carbohydrate or protein intake in the first month of life and cerebral volume at term-equivalent age.

Conclusion: Early cumulative lipid intake in the first month of life is associated with significantly greater cerebellar volume by term-equivalent age in very premature infants. Our findings emphasize the importance of early, aggressive nutrition interventions to optimize cerebellar development in VLBW infants.

Keywords

enteral nutrition; lipids; magnetic resonance imaging; neonates; nutrition; parenteral nutrition; pediatrics

Introduction

The third trimester of pregnancy is marked by an exponential increase in placental nutrient transfer, with fetal fat accretion occurring almost exclusively during this time period.[1] This accumulation of nutrients is vitally important to the rapidly growing fetal brain, which undergoes precisely programmed developmental events during this period, including neuronal migration, complex cortical folding, and synaptogenesis.[2–4] Preterm birth is associated with an abrupt termination of this transplacental nutrition, leaving premature infants vulnerable to growth failure and associated altered brain development during this critical window.[5,6] Additionally, preterm infants are bombarded with noxious stimuli, systemic illness, and inflammation in the extrauterine environment, further predisposing towards abnormal neurosensory experiences, altered brain maturation, and poor neurodevelopmental outcomes.[7–9]

Nutrition interventions in the neonatal intensive care unit (NICU) are continually evolving to prevent extrauterine growth restriction. More aggressive nutrition practices, such as early high-protein parenteral nutrition (PN), early initiation and advancement of enteral feeding, and breast milk fortification, have been implemented in attempts to mimic in-utero nutrient accretion rates and prevent energy deficits.[10,11] Although these changes have led to improvements in postnatal growth rates and neurodevelopmental outcomes, preterm infants continue to experience a high incidence of growth restriction, and the ideal nutrition to optimize brain development in the extrauterine environment remains to be elucidated.[10,12,13]

The successful application of quantitative, 3-dimensional (3D), volumetric magnetic resonance imaging (MRI) tools allow us to accurately and noninvasively measure global and regional volumes of discrete brain regions and tissues. This, in turn, has provided a powerful tool to evaluate the effects of nutrition interventions on preterm brain growth and

development in vivo.[14–17] The aim of this study was to investigate the impact of early macronutrient intake on brain volume by term-equivalent age in a contemporary cohort of preterm infants born at very low-birth-weight (VLBW, <1500 g).

Methods

Participants

Preterm infants admitted to our level IV NICU between June 2012 and April 2017 were enrolled as part of a prospective, observational study of the antecedents and sequelae of prematurity-related brain injury. All infants admitted to our NICU were outborn. Infants were eligible for enrollment if they were born at VLBW (<1500 g) and ≤32 weeks' gestational age and admitted within the first week of life. Infants with a known or suspected brain malformation, dysmorphic features or congenital anomalies suggestive of an underlying genetic syndrome, confirmed metabolic disorder, chromosomal abnormality, or proven perinatal central nervous system infection were excluded. Preterm infants with grade III intraventricular hemorrhage, periventricular hemorrhagic infarction, or cerebellar hemorrhagic injury were also excluded.

Clinical data were extracted from the medical record. Common comorbidities known to affect nutrition advancement and developmental outcomes were also evaluated, including any diagnosis of infection (defined as positive microbial test or ≥7 days of antibiotic treatment), postnatal steroid treatment (hydrocortisone or dexamethasone), moderate-severe bronchopulmonary dysplasia,[18] major surgical intervention (defined as any surgical procedure, including bowel surgery and patent ductus arteriosus ligation), retinopathy of prematurity (beyond stage 2), or surgical necrotizing enterocolitis (requiring laparotomy or drain placement), throughout NICU admission. This study was approved by the Children's National Medical Center Institutional Review Board, and informed, written consent was obtained from the parents of all participants.

Nutrition Intake

Daily nutrition intake (parenteral and enteral) was retrospectively extracted from the electronic medical record, from admission until term-equivalent age. PN with 3-g/kg/d protein (amino acids) was initiated on NICU admission using a standardized premixed starter solution. A 20% soybean oil lipid emulsion (Intralipid 20%) was initiated at 1 g/kg/d within 24 hours of admission. Parenteral protein and lipid administration were advanced by 1 g/kg/d, as tolerated, to a goal of 4 g/kg/d of protein and 3 g/kg/d of lipids.

A standardized feeding protocol for VLBW infants was used, with specific parameters based on birth weight and feeding tolerance. Trophic enteral feeds were initiated at 10–20 mL/kg/d within 24 hours of life or once the infant was deemed clinically stable by the medical team, followed by a daily advancement by 20–30 mL/kg/d, as tolerated, to a goal feeding volume of 160 mL/kg/d. Breast milk was fortified with a commercially available, liquid, bovine-based human milk fortifier to 22 kcal/oz at a feeding volume of 80 mL/kg/d and advanced to 24 kcal/oz at a feeding volume of 100 mL/kg/d. Donor breast milk was made available in our NICU beginning in April 2015 and was provided when maternal breast milk

supply was insufficient and, if parents consented, until 34 weeks' corrected postmenstrual age, at which point infants were transitioned to formula if no maternal breast milk was available.

Cumulative macronutrient and energy intakes for each infant were calculated from recorded nutrition volumes (both enteral and parenteral), with formula content data based on manufacturers' specifications and breast milk content estimated from reference values.[19,20] Energy (kcal) intake calculations were based on the assumption that parenteral carbohydrates provided 3.4 kcal/g, enteral carbohydrates and proteins provided 4 kcal/g, and lipids provided 9 kcal/g.

MRI Acquisition and Processing

Nonsedated brain MRI studies were performed at term-equivalent age on a 3 Tesla MRI scanner (Discovery MR750; General Electric Medical, Systems, Waukesha, WI, USA) with an 8-channel receiver head coil approved for safety in neonates. Infants were immobilized using an InfantVacuum Immobilizer (Newmatic Medical, Caledonia, MI, USA) and provided with double ear protection. The MRI acquisition protocol included structural imaging (T2 3D-cube and T1 3D-spoiled gradient recalled). Volumetric segmentation was performed on Coronal T2 Cube 3D images, using a validated automated algorithm, with subsequent manual inspection and correction as needed by 2 investigators blinded to enteral feeding type (K.O. and K.K.).[21] Interrater reliability measures for manually corrected MRI brain volumes were calculated based on a randomly selected subset of the study cohort, using the intraclass correlation coefficient. Regional brain volumes (in cm^3) were obtained for the cortical gray matter, deep gray matter, white matter, amygdala-hippocampus, cerebellum, and brainstem and utilized to calculate total brain volume for each infant (Figure 1).

Statistical Analysis

Statistical analysis was performed using Statistical Analysis Software (SAS) 9.4. Generalized linear models assessing the effect of macronutrient intake (g/kg/d of carbohydrate, lipid, and protein intake or kcal/kg/d of energy intake) on brain volumes were adjusted for gestational age at birth, postmenstrual age at term-corrected MRI, and average daily weight gain. β-coefficients represented the effect of a 1-g/kg increase in macronutrient intake. Bivariate analyses were performed to assess for significant associations between baseline patient characteristics and medical covariates on regional and total brain volumes. Additional adjustments for significant medical covariates ($P \leq .05$) were subsequently performed. A P-value < .05 was considered significant for all analyses.

Results

Patient Characteristics

A total of 117 VLBW infants admitted to our NICU within the first week of life were recruited. Sixty-seven of these infants were eligible for analysis based on absence of structural brain injury at term-equivalent age, of whom 55 (82.1%) were admitted within the first 48 hours of life. Patient demographics, comorbidities, and growth characteristics

are delineated in Table 1. Average gestational age at birth was 27.60 ± 2.51 weeks, with a mean birth weight spanning 0.96 ± 0.31 kg, with 7 (10.4%) of the patients being small for gestational age at birth. Female infants comprised 61.2% of the study cohort. In analysis of medical covariates, postnatal steroids demonstrated a significant negative association with cerebellar volume, whereas postnatal steroids, retinopathy of prematurity (ROP), and bronchopulmonary dysplasia (BPD) demonstrated a significant negative associated with brainstem volume ($P \leq .05$); number of PN days was not significant when included in generalized linear models. Sex did not have a significant effect on regional or total brain volumes. Interrater reliability of manual MRI brain volume rendering was carried out on 12 randomly selected infants. The intraclass correlation coefficients per patient for the manual correction of MRI volumes were excellent and ranged from 0.94 to 0.99.

Two-Week Cumulative Intake

Cumulative lipid intake in the first 2 weeks of life was significantly associated with increased cerebellar volume ($\beta = 0.096$; $P = 0.007$) at term-equivalent age after adjusting for gestational age at birth, postmenstrual age at term-corrected MRI, and average daily weight gain (Table 2). Positive trends were also seen between lipid intake and brainstem volume, as well as total brain volume, although these did not reach statistical significance ($\beta = 0.008$; $P = .07$ and $\beta = 0.56$; $P = .08$, respectively). Increased cumulative energy intake also demonstrated a borderline-significant relationship with cerebellar volume ($\beta = 0.004$; $P = 0.06$). There were no significant associations between cumulative carbohydrate or protein intake in the first 2 weeks of life and total or regional brain volumes.

Four-Week Cumulative Intake

Cumulative lipid intake in the first 4 weeks of life remained significantly associated with increased cerebellar volume ($\beta = 0.036$; $P = .006$) at term-equivalent age, adjusting for gestational age at birth; postmenstrual age at term-corrected MRI; and average daily weight gain. A significant positive association was found between 4-week lipid intake and brainstem volume ($\beta = 0.004$; $P = .049$), and a positive trend between lipid intake and total brain volume was again seen at 4 weeks ($\beta = 0.209$; $P = .08$). Greater energy intake (kcal) in the first 4 weeks of life was also significantly associated with increased cerebellar volumes ($\beta = 0.006$; $P = .02$). There were no significant associations between cumulative carbohydrate or protein intake in the first 4 weeks of life and total or regional brain volumes.

Additional adjustments for significant medical covariates, based on bivariate analysis, attenuated the associations between cumulative 2- and 4-week lipid intake and cerebellar volumes ($\beta = 0.025–0.07$; $P = .05–.07$), 4-week energy intake and cerebellar volume ($\beta = 0.002$; $P = .13$), and 4-week lipid intake with brainstem volume ($\beta = 0.002$; $P = .33$) (Table 3). Limiting models to significant covariates in multivariable models only ($P < 0.1$) did not change cerebellar associations; however, a more significant positive relationship was noted between 4-week lipid intake and brainstem volume ($\beta = 0.004$; $P = .01$).

Discussion

In our cohort of VLBW infants without structural brain injury, cumulative lipid intake in the first month of life was significantly associated with increased brainstem and cerebellar volume at term-equivalent age. As lipids are the most energy-dense macronutrient, it is not surprising that increased energy intake during this time period was also positively associated with cerebellar volume.

Our study emphasizes the importance of early lipid intake for optimal preterm brain development. In addition to being a dense energy source, lipids perform specific, essential functions for the developing brain. Long-chain polyunsaturated fatty acids, such as docosahexanoic acid and arachidonic acid, make up ≤15%–30% of the brain's dry weight and are involved in important processes, such as retinal development, neurogenesis, and synaptogenesis.[22–24] An adequate provision of cholesterol is also required for normal myelination.[25]

Despite the critical role of dietary fat in preterm brain development, there is a paucity of well-designed, prospective studies investigating the optimal lipid intake for preterm neonates growing in the extrauterine environment. Therefore, current nutrition recommendations are largely extrapolated from fetal accretion rates rather than from demonstrated requirements in preterm neonates growing ex utero.[1,11,26] Additionally, a large proportion of neonates experience deficient or delayed lipid administration, with one study demonstrating that only 34% of infants achieved the recommended lipid intake by the second week of life.[27–32] Part of this insufficient lipid provision may stem from the theoretical risks of unconjugated hyperbilirubinemia, sepsis, thrombocytopenia, and chronic lung disease that were raised in the early days of intravenous lipid-emulsion use in neonates.[26,33,34] Although these theoretical concerns have been unfounded or disproven, many practitioners remain reluctant to optimize early lipid supplementation in preterm infants.[26,33,34]

Studies have demonstrated that the early provision of dietary fats, including initiation of parenteral lipids at doses as high as 3 g/kg/d on the first day of life, and targeted lipid fortification of enteral feeds are well-tolerated with improved neonatal growth velocities. Early lipid intake is associated with improved head growth in preterm infants, which is a surrogate marker of brain size.[32,35,36] Additionally, dit Trolli et al emphasized the neurodevelopmental impact of early lipid intake, demonstrating a positive association between cumulative lipid intake the first 2 weeks of life and developmental quotients in preterm infants at 1 year of age.[37]

In our study, cumulative lipid intake in the first month of life was associated with improved cerebellar and, to a lesser extent, brainstem growth in preterm infants by term-equivalent age. This association remained significant even after accounting for gestational age and weight gain, emphasizing the specific impact of lipid intake on brain growth. These data are consistent with existing studies demonstrating the beneficial impact of early lipid intake on preterm brain development using advanced, quantitative MRI techniques.[14,15,38] Beauport et al evaluated the effect of macronutrient intake in the first 2 weeks of life on brain injury in preterm neonates at term-equivalent age, with greater fat intake correlating to less

severe brain injury.[14] In the same cohort, serial MRI studies demonstrated an increasingly robust relationship between cumulative energy and lipid intake in the first 2 weeks of life and cerebellar, basal nuclei, and total brain volumes by term-equivalent age.[38] Although we also saw a positive trend between 2-week lipid intake and total brain volumes, this relationship did not achieve statistical significance ($P = .08$), potentially reflecting our cohort's comparatively wider variation in birth weight and gestational age, as well as greater incidence of significant medical comorbidities. The positive association between lipid intake and brain volumes at 4 weeks of age seen in our study are consistent with the findings of Coviello et al, who demonstrated a significant positive association between cumulative lipid intake in the first 28 days of life and cerebellar, basal ganglia and thalamic volumes.[15] In contrast to these positive findings, studies of average macronutrient intake in preterm infants did not find a significant relationship between lipid intake and total or regional brain volumes at term-equivalent age.[39,40] This discrepancy between average vs cumulative lipid intake in relation to brain growth warrants further investigation as we continue to explore the ideal lipid intake for optimal brain growth in the preterm population.

The positive relationship between lipid intake and cerebellar growth is of extreme interest, as the cerebellum is the most rapidly growing brain structure during the second half of pregnancy, with healthy fetuses experiencing a remarkable 34-fold increase in cerebellar volume that far exceeds the growth of the cerebrum during this time period.[2–4] In the preterm infant, this accelerated growth and development make the cerebellum particularly susceptible to injury, with an incidence of ≤19% in very premature infants.[41–43] Even in the absence of overt cerebellar injury, premature neonates demonstrate slower cerebellar and brainstem growth compared with healthy control fetuses in the third trimester, as well as altered cerebellar microstructural development and metabolite levels, suggesting that these regions may be especially vulnerable to postnatal insults, such as nutrition deficits.[6,44–46] Alterations in cerebellar and brainstem growth may have extensive and far-reaching consequences for supratentorial development via increasingly recognized cerebro-ponto-cerebellar connectivity and trophic transsynaptic interactions.[43,47] Additionally, in preterm infants, cerebellar size at term-equivalent age has been positively associated with improved cognitive, language, and motor scores at 2 years of age.[48,49] Indeed, emerging evidence highlights important implications of postnatal cerebellar development on long-term neurodevelopmental outcomes in preterm infants in critical areas, such as language and cognition.[47,50]

There are several strengths of this study; however, our limitations should be noted. Cumulative macronutrient and energy intake from breast milk were not directly measured but rather estimated based on recorded nutrition volumes and reference values. The retrospective nature of our clinical and nutrition data collection could lead to potential con-founding, especially with medical comorbidities that were broadly categorized, and also preclude us from controlling for the variability in macronutrient administration between patients. It is possible that the attenuation of our findings, after controlling for medical covariates, could be related to our relatively small sample size in relation to the number of covariates assessed. It is also difficult to accurately control for the complex, multifactorial interactions that influence brain growth in a retrospective manner; however,

the identification of these covariates with potential impact on brain development will be important to factor into future large, prospective, randomized studies of nutrition intake.

Conclusion

This study of macronutrient intake in VLBW preterm infants demonstrates a significant positive relationship between cumulative lipid intake in the first month of life and volumetric brain growth on term-equivalent MRI, specifically in the brainstem and rapidly developing cerebellum. These findings highlight the vital importance of dietary lipids for the developing preterm brain. In addition to the ideal total lipid intake, several questions remain regarding the optimal balance in quality and type of lipids to provide for preterm infants throughout the early postnatal period. Further investigation is warranted into the neurodevelopmental effects of newer intravenous lipid emulsions and targeted enteral lipid fortification. Future high-quality, prospective trials are needed to further elucidate the optimal provision of lipids for preterm infants to promote postnatal brain growth and improve long-term neurodevelopment.

Financial Disclosure:

This project was support by award numbers UL1TR001876, 1U54HD090257, and R01HL116585-01 from the National Institutes of Health (NIH) National Center for Advancing Translational Sciences; The District of Columbia Intellectual Developmental Disabilities Research Center at Children's National, supported through the NIH; Eunice Kennedy Shriver National Institute of Child Health and Human Development program grant; and the National Heart, Lung, and Blood Institute.

References

1. Haggarty P Fatty acid supply to the human fetus. Annu Rev Nutr. 2010;30(1):237–255. [PubMed: 20438366]
2. Clouchoux C, Kudelski D, Gholipour A, et al. Quantitative in vivo MRI measurement of cortical development in the fetus. Brain Struct Funct. 2012;217(1):127–139. [PubMed: 21562906]
3. Clouchoux C, Guizard N, Evans AC, du Plessis AJ, Limperopoulos C. Normative fetal brain growth by quantitative in vivo magnetic resonance imaging. Am J Obstet Gynecol. 2012;206(2):173.e1–173.e8. [PubMed: 22055336]
4. Andescavage NN, du Plessis A, McCarter R, et al. Complex trajectories of brain development in the healthy human fetus. Cereb Cortex. 2017;27(11):5274–5283. [PubMed: 27799276]
5. Matthews LG, Walsh BH, Knutsen C, et al. Brain growth in the NICU: critical periods of tissue-specific expansion. Pediatr Res. 2018;83(5):976–981. [PubMed: 29320484]
6. Bouyssi-Kobar M, du Plessis AJ, McCarter R, et al. Third trimester brain growth in preterm infants compared with in utero healthy fetuses. Pediatrics. 2016;138(5):e20161640. [PubMed: 27940782]
7. Guellec I, Lapillonne A, Marret S, et al. Effect of intra- and extrauterine growth on long-term neurologic outcomes of very preterm infants. J Pediatr. 2016;175:93–99.e1. [PubMed: 27318373]
8. Walker SM. Biological and neurodevelopmental implications of neonatal pain. Clin Perinatol. 2013;40(3):471–491. [PubMed: 23972752]
9. Patra A, Huang H, Bauer JA, Giannone PJ. Neurological consequences of systemic inflammation in the premature neonate. Neural Regen Res. 2017;12(6):890–896. [PubMed: 28761416]
10. Horbar JD, Ehrenkranz RA, Badger GJ, et al. Weight growth velocity and postnatal growth failure in infants 501 to 1500 grams: 2000–2013. Pediatrics. 2015;136(1):e84–e92. [PubMed: 26101360]
11. Agostoni C, Buonocore G, Carnielli VP, et al. Enteral nutrient supply for preterm infants: commentary from the european society of paediatric gastroenterology, hepatology and nutrition committee on nutrition. J Pediatr Gastroenterol Nutr. 2010;50(1):85–91. [PubMed: 19881390]

12. Franz AR, Pohlandt F, Bode H, et al. Intrauterine, early neonatal, and postdischarge growth and neurodevelopmental outcome at 5.4 years in extremely preterm infants after intensive neonatal nutritional support. Pediatrics. 2009;123(1):e101–e109. [PubMed: 19117831]
13. Ehrenkranz RA, Das A, Wrage LA, et al. Early nutrition mediates the influence of severity of illness on extremely LBW infants. Pediatr Res. 2011;69(6):522–529. [PubMed: 21378596]
14. Beauport L, Schneider J, Faouzi M, et al. Impact of early nutritional intake on preterm brain: a magnetic resonance imaging study. J Pediatr. 2017;181:29–36. [PubMed: 27837953]
15. Coviello C, Keunen K, Kersbergen KJ, et al. Effects of early nutrition and growth on brain volumes, white matter microstructure, and neurodevelopmental outcome in preterm newborns. Pediatr Res. 2018;83(1):102–110. [PubMed: 28915232]
16. Tam EW, Chau V, Barkovich AJ, et al. Early postnatal docosahexaenoic acid levels and improved preterm brain development. Pediatr Res. 2016;79(5):723–730. [PubMed: 26761122]
17. Kamino D, Studholme C, Liu M, et al. Postnatal polyunsaturated fatty acids associated with larger preterm brain tissue volumes and better outcomes. Pediatr Res. 2018;83(1):93–101. [PubMed: 28915231]
18. J Jobe AH, Bancalari E. Bronchopulmonary dysplasia. Am J Respir Crit Care Med. 2001;163(7):1723–1729. [PubMed: 11401896]
19. Wojcik KY, Rechtman DJ, Lee ML, Montoya A, Medo ET. Macronutrient analysis of a nationwide sample of donor breast milk. J Am Diet Assoc. 2009;109(1):137–140. [PubMed: 19103335]
20. RE Kleinman, FR Greer, eds. Pediatric Nutrition. 7th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2014.
21. Makropoulos A, Gousias IS, Ledig C, et al. Automatic whole brain MRI segmentation of the developing neonatal brain. IEEE Trans Med Imaging. 2014;33(9):1818–1831. [PubMed: 24816548]
22. Tanaka K, Farooqui AA, Siddiqi NJ, Alhomida AS, Ong WY. Effects of docosahexaenoic acid on neurotransmission. Biomol Ther. 2012;20(2):152–157.
23. McNamara RK, Vannest JJ, Valentine CJ. Role of perinatal long-chain omega-3 fatty acids in cortical circuit maturation: mechanisms and implications for psychopathology. World J Psychiatry. 2015;5(1):15–34. [PubMed: 25815252]
24. Harris WS, Baack ML. Beyond building better brains: bridging the docosahexaenoic acid (DHA) gap of prematurity. J Perinatol. 2015;35(1):1–7. [PubMed: 25357095]
25. Saher G, Brugger B, Lappe-Siefke C, et al. High cholesterol level is essential for myelin membrane growth. Nat Neurosci. 2005;8(4):468–475. [PubMed: 15793579]
26. Salama GS, Kaabneh MA, Almasaeed MN, Alquran MI. Intravenous lipids for preterm infants: a review. Clin Med Insights Pediatr. 2015;9:25–36. [PubMed: 25698888]
27. Ibrahim HM, Jeroudi MA, Baier RJ, Dhanireddy R, Krouskop RW. Aggressive early total parental nutrition in low-birth-weight infants. J Perinatol. 2004;24(8):482–486. [PubMed: 15167885]
28. Drenckpohl D, McConnell C, Gaffney S, Niehaus M, Macwan KS. Randomized trial of very low birth weight infants receiving higher rates of infusion of intravenous fat emulsions during the first week of life. Pediatrics. 2008;122(4):743–751. [PubMed: 18829797]
29. Lapillonne A, Fellous L, Mokthari M, Kermorvant-Duchemin E. Parenteral nutrition objectives for very low birth weight infants: results of a national survey. J Pediatr Gastroenterol Nutr. 2009;48(5):618–626. [PubMed: 19367179]
30. Ng DV, Brennan-Donnan J, Unger S, et al. How close are we to achieving energy and nutrient goals for very low birth weight infants in the first week? JPEN. 2017;41(3):500–506.
31. Robinson DT, Martin CR. Fatty acid requirements for the preterm infant. Semin Fetal Neonatal Med. 2017;22(1):8–14. [PubMed: 27599697]
32. Fischer CJ, Maucort-Boulch D, Essomo Megnier-Mbo CM, Remontet L, Claris O. Early parenteral lipids and growth velocity in extremely-low-birth-weight infants. Clin Nutr. 2014;33(3):502–508. [PubMed: 23958274]
33. Alwaidh MH, Bowden L, Shaw B, Ryan SW. Randomised trial of effect of delayed intravenous lipid administration on chronic lung disease in preterm neonates. J Pediatr Gastroenterol Nutr. 1996;22(3):303–306. [PubMed: 8708885]

34. Lapillonne A, Fellous L, Kermorvant-Duchemin E; French neonatal departments. Use of parenteral lipid emulsions in french neonatal ICUs. Nutr Clin Pract. 2011;26(6):672–680. [PubMed: 22205555]
35. Peiler A, Woelfle J, Stutte S, Schreiner F, Bartmann P, Gohlke B. Postnatal nutrition in extremely low birth weight infants and its impact on growth until the age of 6 years. Acta Paediatr. 2014;103(2):e61–e68. [PubMed: 24127881]
36. Morgan C, McGowan P, Herwitker S, Hart AE, Turner MA. Postnatal head growth in preterm infants: a randomized controlled parenteral nutrition study. Pediatrics. 2014;133(1):e120–e128. [PubMed: 24379229]
37. dit Trolli SE, Kermorvant-Duchemin E, Huon C, Bremond-Gignac D, Lapillonne A. Early lipid supply and neurological development at one year in very low birth weight (VLBW) preterm infants. Early Hum Dev. 2012;88 (suppl 1):S25–S29.
38. Schneider J, Fischer Fumeaux CJ, Duerden EG, et al. Nutrient intake in the first two weeks of life and brain growth in preterm neonates. Pediatrics. 2018;141(3):e20172169. [PubMed: 29440285]
39. Paviotti G, De Cunto A, Zennaro F, et al. Higher growth, fat and fat-free masses correlate with larger cerebellar volumes in preterm infants at term. Acta Paediatr. 2017;106(6):918–925. [PubMed: 28295577]
40. Power VA, Spittle AJ, Lee KJ, et al. Nutrition, growth, brain volume, and neurodevelopment in very preterm children. J Pediatr. 2019;215:50–55.e3. [PubMed: 31561956]
41. Steggerda SJ, Leijser LM, Wiggers-de Bruine FT, van der Grond J, Walther FJ, van Wezel-Meijler G. Cerebellar injury in preterm infants: incidence and findings on US and MR images. Radiology. 2009;252(1):190–199. [PubMed: 19420320]
42. Volpe JJ. Cerebellum of the premature infant: rapidly developing, vulnerable, clinically important. J Child Neurol. 2009;24(9):1085–1104. [PubMed: 19745085]
43. Limperopoulos C, Soul JS, Haidar H, et al. Impaired trophic interactions between the cerebellum and the cerebrum among preterm infants. Pediatrics. 2005;116(4):844–850. [PubMed: 16199692]
44. Brossard-Racine M, Poretti A, Murnick J, et al. Cerebellar microstructural organization is altered by complications of premature birth: a case-control study. J Pediatr. 2017;182:28–33. [PubMed: 27843009]
45. Limperopoulos C, Soul JS, Gauvreau K, et al. Late gestation cerebellar growth is rapid and impeded by premature birth. Pediatrics. 2005;115(3):688–695. [PubMed: 15741373]
46. Brossard-Racine M, Murnick J, Bouyssi-Kobar M, Coulombe J, Chang T, Limperopoulos C. Altered cerebellar biochemical profiles in infants born prematurely. Sci Rep. 2017;7(1):8143. [PubMed: 28811513]
47. Limperopoulos C, Bassan H, Gauvreau K, et al. Does cerebellar injury in premature infants contribute to the high prevalence of long-term cognitive, learning, and behavioral disability in survivors? Pediatrics. 2007;120(3):584–593. [PubMed: 17766532]
48. Cheong JL, Thompson DK, Spittle AJ, et al. Brain volumes at term-equivalent age are associated with 2-year neurodevelopment in moderate and late preterm children. J Pediatr. 2016;174:91–97.e1. [PubMed: 27174146]
49. Van Kooij BJ, Benders MJ, Anbeek P, et al. Cerebellar volume and proton magnetic resonance spectroscopy at term, and neurodevelopment at 2 years of age in preterm infants. Dev Med Child Neurol. 2012;54(3):260–266. [PubMed: 22211363]
50. Allin M, Matsumoto H, Santhouse AM, et al. Cognitive and motor function and the size of the cerebellum in adolescents born very preterm. Brain. 2001;124(Pt 1):60–66. [PubMed: 11133787]

Clinical Relevancy Statement

Very low-birth-weight infants (<1500 g) are at high risk for postnatal growth failure and neurodevelopmental impairment. Lipids are a critical source of energy and play a vital role in central nervous system development; however, few studies have investigated the optimal lipid intake for brain growth and development in this population. In this study, we use quantitative MRI to demonstrate a significant association between lipid intake in the first month of life and brain growth at term-equivalent age in preterm infants, particularly in the rapidly growing cerebellum. Our findings emphasize the importance of early, aggressive lipid intake in preterm infants, as well as the need for future research to establish goals for lipid administration to optimize neurodevelopment in this vulnerable population.

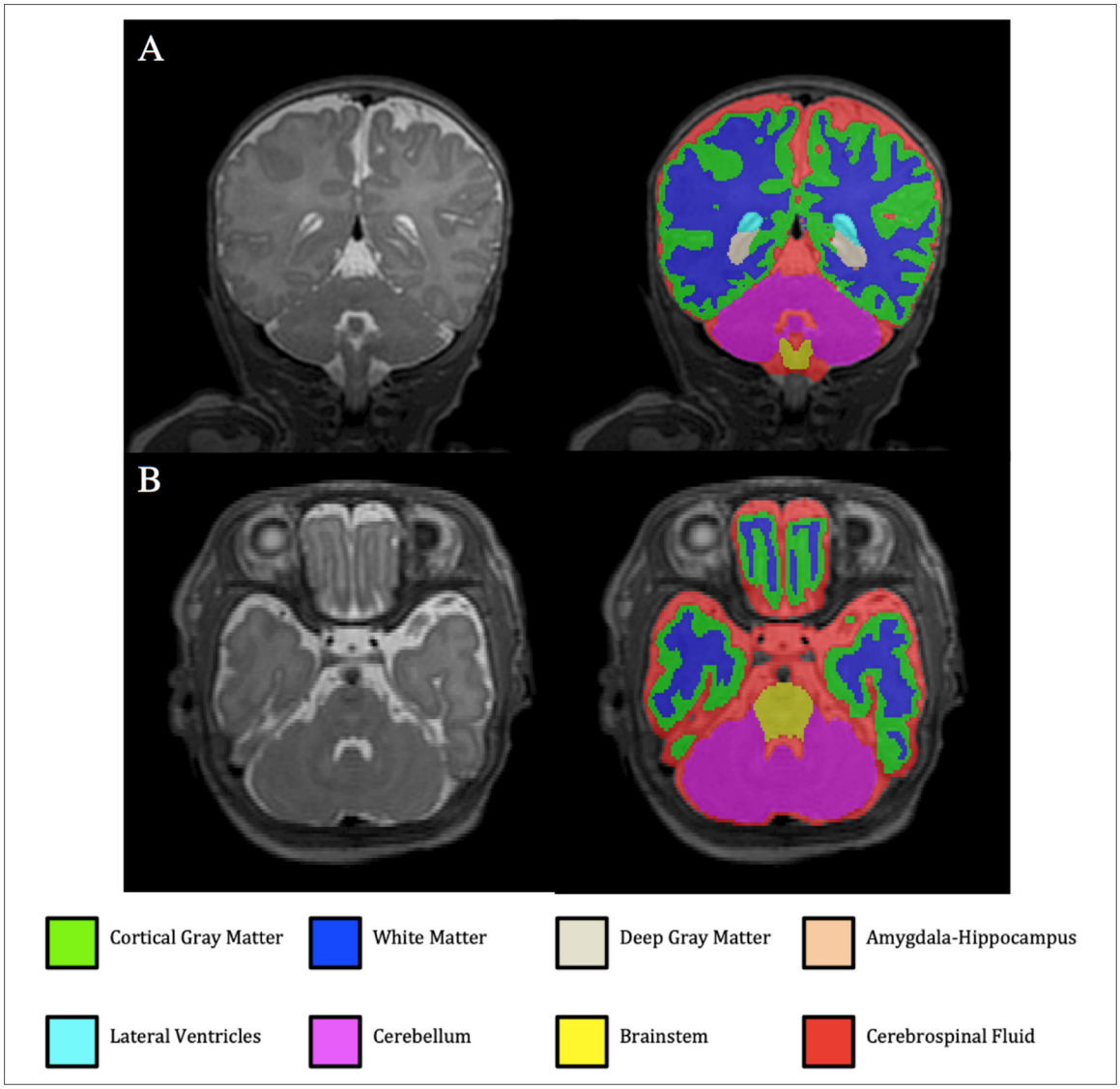

Figure 1.
(A) Coronal and (B) axial views of neonatal brain with volumetric segmentation.

Table 1.

Clinical Characteristics of the Preterm Cohort.

Patient Characteristic (n = 67)	Mean (SD), Median (IQR), or N (%)
Admission ≤48 hours of birth (n, %)	55 (82.1)
Female sex, n, (%)	41 (61.2)
Gestational age at birth, wk	27.60 (2.51)
Birth weight, kg	0.96 (0.31)
Birth head circumference, cm	24.08 (2.63)
Small for gestational age at birth, n (%)	7 (10.4)
Average weight gain, g/d	20.65 (4.65)
Infection, n (%)	43 (64.2)
Postnatal steroids, n (%)	25 (37.3)
Bronchopulmonary dysplasia, n (%)	26 (38.8)
Surgery, n (%)	27 (40.3)
Retinopathy of prematurity beyond stage 2, n (%)	22 (32.8)
Surgical necrotizing enterocolitis, n (%)	6 (9.0)
Gestational age at MRI, wk	40.12 (1.72)
Enteral type (n, %)	
Maternal breast milk	30 (44.8)
Donor breast milk	13 (19.4)
Formula	24 (35.8)
Average macronutrient intake	
Carbohydrate, g/kg/d	12.3 (11.1, 13.6)
Lipid, g/kg/d	4.0 (3.1, 5.3)
Protein, g/kg/d	3.9 (3.6, 4.2)
Energy, kcal/kg/d	99.0 (90.0, 111.0)
Total parenteral nutrition days	25.0 (11.0, 41.0)
Time to full enteral feeds	27.0 (16.0, 41.0)
Total nutrition days	74.0 (51.0, 99.0)

IQR, interquartile range; MRI, magnetic resonance imaging.

Table 2.

Association Between Cumulative Macronutrient and Energy Intake in the First Month of Life and Total and Regional Brain Volumes.

	Cumulative Macronutrient Intake[a]							
	Carbohydrate		Lipid		Protein		Energy (kcal)	
Brain Volume Measures (cm^3)	β ($\times 10^3$)	*P*	B ($\times 10^3$)	*P*	B ($\times 10^3$)	*P*	B ($\times 10^3$)	*P*
2 Weeks								
Total brain volume	−18.6	0.90	557.1	0.08	−283.9	0.43	19.6	0.35
White matter	−38.1	0.62	234.8	0.15	−210.8	0.25	5.9	0.58
Cerebellum	5.4	0.75	95.8	<0.01	−13.2	0.74	4.4	0.06
Cortical gray matter	21.8	0.72	175.1	0.18	−34.4	0.82	7.8	0.37
Deep gray matter	−7.5	0.52	40.4	0.10	−25.0	0.37	1.0	0.55
Amygdala-hippocampus	−0.4	0.74	3.3	0.19	−0.2	0.94	0.1	0.54
Brainstem	0.2	0.93	8.4	0.07	0.3	0.95	0.4	0.23
4 Weeks								
Total brain volume	37.1	0.61	209.2	0.08	−144.5	0.65	17.9	0.14
White matter	12.6	0.73	81.7	0.18	−62.0	0.71	6.9	0.27
Cerebellum	3.0	0.71	36.1	<0.01	8.0	0.83	3.1	0.02
Cortical gray matter	17.1	0.56	72.5	0.14	−90.9	0.49	6.1	0.23
Deep gray matter	4.2	0.45	13.1	0.15	1.7	0.95	1.4	0.14
Amygdala-hippocampus	0.2	0.78	1.6	0.10	−0.6	0.82	0.1	0.21
Brainstem	0.4	0.73	3.5	[b]0.05	2.0	0.68	0.3	0.09

[a]Results of generalized linear models adjusted for gestational age at birth, postmenstrual age at MRI, and average daily weight gain; β estimates represent effect of a 1-g/kg increase in macronutrient intake.

[b]*P*-value of .049, rounded to nearest decimal place.

Table 3.

Additional Adjustment for Significant Medical Covariates (Based on Bivariate Analysis).

	Exposures[a]								
	Macronutrient		Weight Gain		Steroids		Retinopathy of Prematurity (ROP)		Bronchopulmonary Dysplasia (BPD)	
Brain Volume Measures (cm^3)	**B ($\times 10^3$)**	***P***	**B ($\times 10^3$)**	***P***	**B ($\times 10^3$)**	***P***	**B ($\times 10^3$)**	***P***	**B ($\times 10^3$)**	***P***
Lipid Intake *(2 Week)*										
Cerebellum	70.4	0.05	151.8	0.10	−2088.1	0.05				
Lipid Intake *(4 Week)*										
Cerebellum	25.3	0.07	127.7	0.18	−1963.8	0.07				
Brainstem	1.8	0.33	16.6	0.17	−200.8	0.14	−213.5	0.09	−351.6	0.004
Energy Intake *(4 Week)*										
Cerebellum	2.1	0.13	136.4	0.15	−2265.4	0.03				

[a]Results of generalized linear models adjusted for GA at birth, GA at MRI, weight gain, and medical risks significant in bivariate analyses; β estimates represent effect of a 1-g/kg increase in macronutrient intake.

JPEN J Parenter Enteral Nutr. Author manuscript; available in PMC 2021 October 07.