THE LEARNING LEAD
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Nutrition for Fast and Efficient Connections in the Brain

Behaviors, perceptions, and higher cognitive functions are all regulated by our brain. In order to exert such centralized control, the brain requires organized and efficient brain connectivity,[1] which in turn is needed for efficient brain communication (e.g., processing incoming and outgoing information).[2] Those strong, fast, and efficient connections mainly develop and mature after birth and during early childhood. Many factors influence their development, including genetic, biological, and environmental factors. What is the role of nutrition in the formation and maturation of fast and efficient brain connections?

The Role of Nutrients in Brain Development

Nutrients can play a role at several stages of building an efficient brain (e.g., by supporting cell structures, being involved in signaling processes, and providing energy to build and maintain brain connections). Nutrients have been linked to several neurodevelopmental processes; e.g., nutrients that impact brain anatomy include iodine, zinc, copper, choline, vitamin A, and long-chain polyunsaturated fatty acids (LC-PUFAs); nutrients that affect neurotransmitter function include protein, iron, zinc, copper, and choline; and nutrients that support oxidative and glycolytic metabolism and that are in high demand in the developing brain include glucose, protein, iron, and zinc.[3] Phospholipids (PLs) are structural components of neural tissues and their peak rate of accretion overlaps with neurodevelopmental milestones.[4]

One of the brain connectivity-related neurodevelopmental processes that peaks during infancy and childhood is myelination, the ensheathment of axons with a lipid-rich myelin sheath. Myelination is an expression of the functional maturity of the brain and a cornerstone of human neurodevelopment.[5,6] It has been shown to be associated with cognitive performance in infants and children[7] as well as in adults.[8]

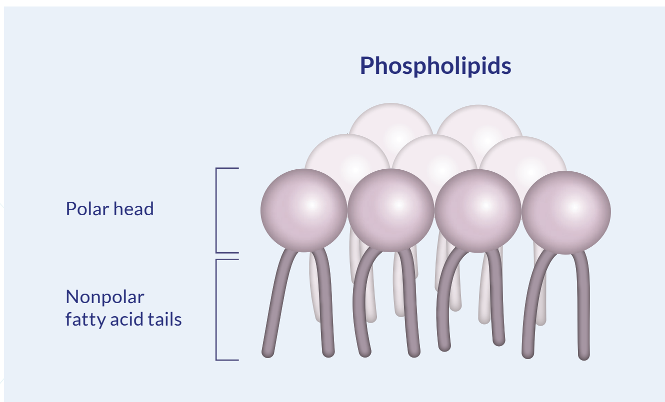
Specific Nutrients for Myelination & Connectivity

MICRONUTRIENTS AND FATTY ACIDS

Nutritional deficiencies in vitamin B_9, vitamin B_{12},[9] iron and transferrin,[10,11] choline, and LC-PUFAs like docosahexaenoic acid (DHA)[12] have been reported to severely reduce myelination, alter myelin composition, or decrease myelin synthesis.[13] DHA, for example, is important for myelin structure,[12] synaptogenesis,[12] and plasticity.[14]

Observational human findings describe differences in myelin and cognitive development between breastfed and formula-fed infants[15,16] and suggest a role of vitamin B_9, vitamin B_{12}, iron, DHA, arachidonic acid (ARA), sphingomyelin (SM), and phosphatidylcholine (PC) from infant nutrition in myelin development.[16] Preclinical studies support the contribution of those nutrients, alone and in combination, to different steps of myelination during development, particularly for a blend containing DHA, ARA, vitamin B_9, vitamin B_{12}, iron, and SM.[17] Furthermore, nervonic acid and lignoceric acid content may play a role in myelin development, as a study showed reduced levels in brain white matter of formula-fed versus breastfed infants in the first 6 months of life.[18]

POLAR LIPIDS



Polar lipids (e.g., PLs and sphingolipids) play an important role as critical structural components of cell membranes and functional contributors to neurotransmission, myelination, and brain connectivity.[4,19] Polar lipids are lipids with a polar head and a nonpolar tail[20,21] and include mainly PLs and sphingolipids. They are abundant in the developing brain, present in breastmilk, and emerging science indicates a potential role of dietary intake of those lipids for brain and cognitive development, particularly in relation to myelination and connectivity:

- **Phospholipids (PLs):** Mainly distributed into 5 classes—phosphatidylinositol (PI), phosphatidylethanolamine (PE), phosphatidylserine (PS), phosphatidylcholine (PC), and sphingomyelin (SM).[22] They are important structural myelin lipids and provide functionally crucial signaling lipids in myelin.[23] The most abundant PLs in the fat in breastmilk are SM and PC.[24,25]

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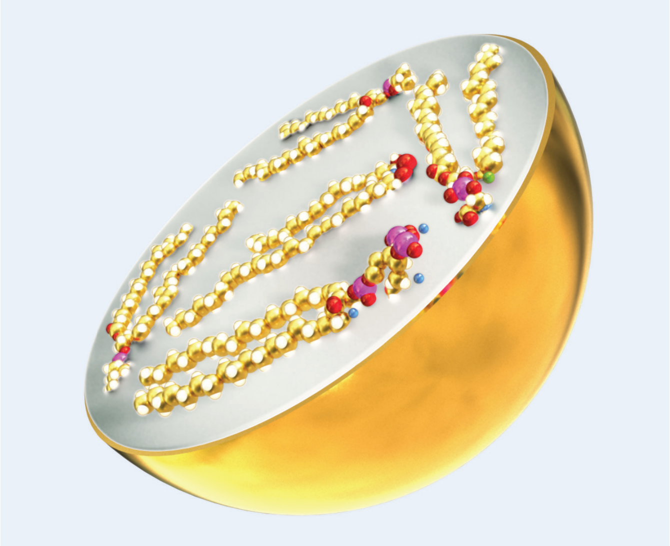
- **Sphingomyelin (SM):** One of the most abundant lipids in the brain and one of the most abundant sphingophospholipids in breastmilk.[26] The effect of dietary SM was demonstrated in preclinical studies and in a pilot study in very low birthweight, preterm babies, where those given SM-fortified infant formula (in addition to breastmilk) showed some improved behavior rating scores, information processing, and sustained attention at 18 months of age compared to a control milk (in addition to breastmilk).[27] The specific association of dietary SM to myelination development in healthy children was reported in an observational study, where higher levels of SM in infant nutrition were significantly correlated with higher levels of myelin content at 12–24 months and more prolonged rates of myelination in different brain areas. Additional cell findings indicate oligodendrocyte maturation and increased axon myelination as potential mechanisms of action.[28]
- **Gangliosides:** Brain-enriched glycosphingolipids with sialic acid residues. Gangliosides are involved in synaptic networking, dendritic branching, and cell multiplication and migration during neonatal development[29]—processes that are important for building fast and efficient connections. Gangliosides are critical in neurodevelopment and the integrity of the nervous system,[30] and contribute to myelination by acting as “communicators” among the myelin lipids.[23] Preclinical dietary supplementation of diet or milk lipids enriched in gangliosides and PLs showed benefits to memory and learning[31] and speed and accuracy.[32] Human infant studies investigating infant formula supplemented with complex milk lipids containing gangliosides and PLs showed benefits to hand and eye coordination, performance, and general neurodevelopment at 6 months of age. However, their scores did not differ from those of a reference group of breastfed infants.[33]

Milk PLs are also important sources or carriers of relevant neurodevelopment components, like LC-PUFAs and choline.[34] About 0.2–2% of fatty acids in human milk are found in molecules such as PLs, gangliosides, and cholesterol.[22]

Sources of Polar Lipids in Infant Nutrition



Sources of polar lipids for infants are breastmilk and infant nutrition. Polar lipid concentrations and proportions vary greatly in breastmilk, depending on the method of milk expression or analysis, the lactation period, and maternal diet during lactation.[4]

In milk, lipids are secreted in the form of fat globules with a core of triacylglycerides, bounded by polar PLs, and the entire globule is bounded by a membrane composed of significant quantities of, for example, PLs, gangliosides, and SM.[22,35,36] In infant formula, polar lipids can come from different ingredients, such as PL complexes or a specific alpha-lactalbumin whey protein concentrate. The latter can be a rich source of PLs and SM when using a specific process that retains the polar lipids[37] and can result in SM levels similar to those of breastmilk.[38]

REFERENCES

1. Jiang X, Nardelli J. *Neurobiol Dis.* 2016;92(Pt A):3-17.
2. Puppo F, George V, Silva GA. *Sci Rep.* 2018;8:10460.
3. Georgieff MK, Ramel SE, Cusick SE. *Acta Paediatr.* 2018;107(8):1310-21.
4. Zheng L, Fleith M, Giuffrida F, O'Neill BV, Schneider N. *Adv Nutr.* 2019;10(6):1163-76.
5. Barkovich AJ. *J Inherit Metab Dis.* 2005;28(3):311-43.
6. Dean DC III, O'Muircheartaigh J, Dirks H, et al. *Neuroimage.* 2014;84:742-52.
7. Deoni SCL, O'Muircheartaigh J, Elison JT, et al. *Brain Struct Funct.* 2014;221:1189-203.
8. Scholz J, Klein MC, Behrens TEJ, Johansen-Berg H. *Nat Neurosci.* 2009;12(11):1370-1.
9. Black RE, Allen LH, Bhutta ZA, et al. *Lancet.* 2008;371(9608):243-60.
10. Lozoff B, Jimenez E, Smith JB. *Arch Pediatr Adolesc Med.* 2006;160(11):1108-13.
11. Beard JL, Connor JR. *Annu Rev Nutr.* 2003;23:41-58.
12. Georgieff MK. *Am J Clin Nutr.* 2007;85(2):614S-20S.
13. Prado EL, Dewey KG. *Nutr Rev.* 2014;72(4):267-84.
14. McNamara RK. *Prostaglandins Leukot Essent Fatty Acids.* 2013;88(1):33-42.
15. Deoni SC, Dean DC III, Piryatinsky I, et al. *Neuroimage.* 2013;82:77-86.
16. Deoni S, Dean D III, Joelson S, O'Regan J, Schneider N. *Neuroimage.* 2018;178:649-59.
17. Hauser J, Sultan S, Rytz A, Steiner P, Schneider N. *Nutr Neurosci.* 2019:1-15.
18. Farquharson J, Jamieson EC, Logan RW, et al. *Prenat Neonat Med.* 1996;1:234-40.
19. Palmano K, Rowan A, Guillermo R, Guan J, McJarrow P. *Nutrients.* 2015;7(5):3891-913.
20. Belhocine TZ, Prato FS. *EJNMMI Res.* 2011;1(1):17.
21. Alberts B, Johnson A, Lewis J, et al. *Molecular Biology of the Cell.* 4th ed. New York: Garland Science; 2002.
22. Giuffrida F, Cruz-Hernandez C, Bertschy E, et al. *Nutrients.* 2016;8(11):715.
23. Schmitt S, Castelvetri LC, Simons M. *Biochim Biophys Acta.* 2015;1851(8):999-1005.
24. Cilla A, Quintaes KD, Barbera R, Alegria A. *Crit Rev Food Sci Nutr.* 2016;56(11):1880-92.
25. Thakkar SK, Giuffrida F, Cruz-Hernandez C, et al. *Am J Hum Biol.* 2013;25(6):770-9.
26. Norton WT, Cammer W. *Myelin.* 2nd ed. New York: Plenum. 1984:147-80.
27. Tanaka K, Hosozawa M, Kudo N, et al. *Brain Dev.* 2013;35(1):45-52.
28. Schneider N, Hauser J, Oliveira M, et al. *eNeuro.* 2019;6(4).
29. Wang B. *Adv Nutr.* 2012;3(3):465S-72S.
30. Yu RK, Tsai YT, Ariga T. *Neurochem Res.* 2012;37(6):1230-44.
31. Vickers MH, Guan J, Gustavsson M, et al. *Nutr Res.* 2009;29(6):426-35.
32. Liu H, Radlowski EC, Conrad MS, Li Y, Dilger RN, Johnson RW. *J Nutr.* 2014;144(12):1903-9.
33. Gurnida DA, Rowan AM, Idjradinata P, Muchtadi D, Sekarwana N. *Early Hum Dev.* 2012;88(8):595-601.
34. Ingvordsen Lindahl IE, Artegoitia VM, Downey E, et al. *Nutrients.* 2019;11(2):222.
35. Giuffrida F, Cruz-Hernandez C, Flück B, et al. *Lipids.* 2013;48(10):1051-8.
36. German JB. *Matern Child Nutr.* 2011;7(suppl 2):2-16.
37. MacFarland B, Bettler J, Moloney C, et al. *Adv Nutr.* 2017;8(1):17.
38. Moloney C, Walshe E, Phelan M, et al. *Int Dairy J.* 2018;78:138-44.