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The Fats of life in early childhood brain development

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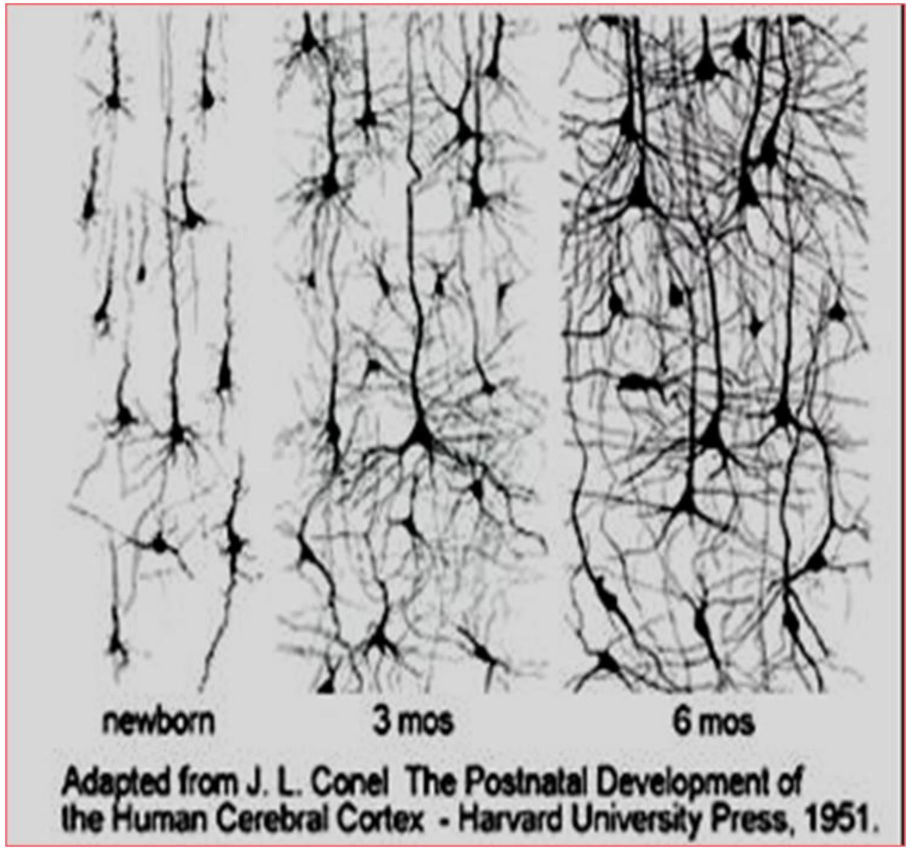
Objectives

- Understand the importance of nutrition in structural neurodevelopment and brain signaling in early life
- The role of specific nutrients in brain function and development
  - Lipids: Phospholipids and Sphingomyelin
- Clinical evidence in infants and children
- The role of Pediatricians in advancing the health of children

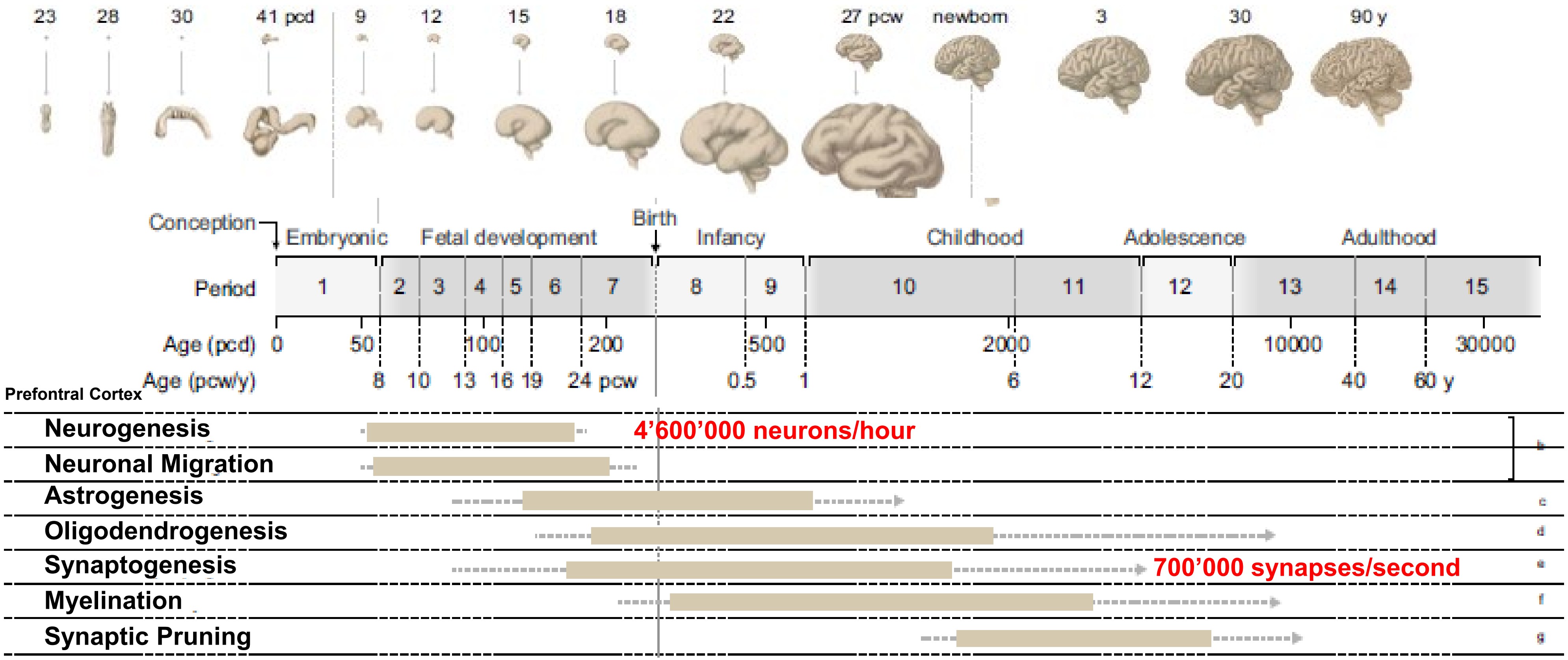
Development of Synapse (Intelligence)



"WE SEE HOW EARLY CHILDHOOD EXPERIENCES ARE SO IMPORTANT TO LIFELONG OUTCOMES, HOW THE EARLY ENVIRONMENT LITERALLY BECOMES EMBEDDED IN THE BRAIN AND CHANGES ITS ARCHITECTURE."

- Andrew S. Garner

Timeline of Key Human Neurodevelopmental Processes



1. Adapted from Silbereis et al., Neuron, 2016

Nature & Nurture

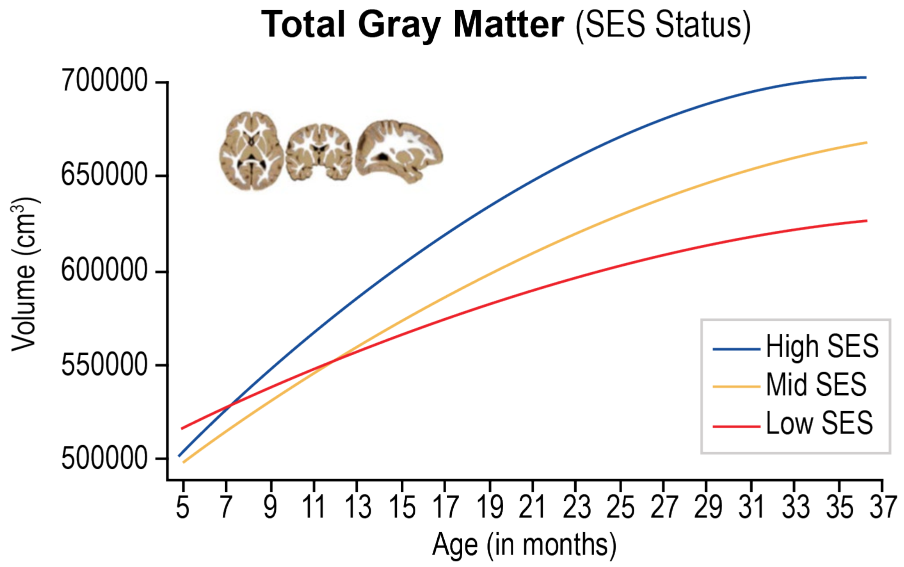
General

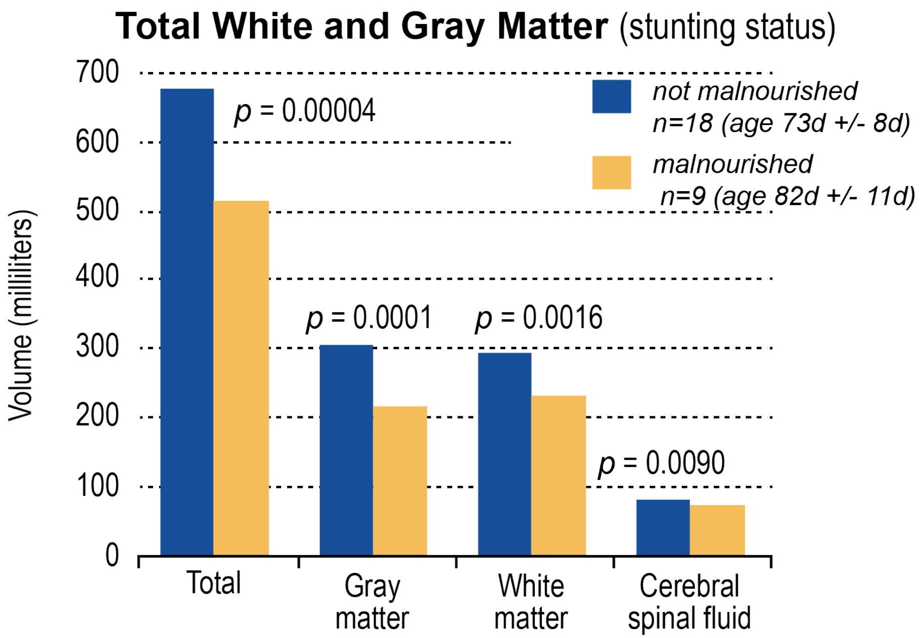
- **Gene expression** (nature)
- **Environmental factors** (nurture)

→ molecular cues guide development & are dependent upon the experiences of the developing child

Environmental Factors

- Socioeconomic status
- Nutritional status
- Social Interactions
- Urbanization
- Pollution
- Social mobility
- Stress





Source: worldbank.org/en/publication/WDR 2018 team, using data from Nelson and others (2017). Data at http://bit.do/WDR2018-Fig_S2-1.

Nutrients that influence brain development & functions

- DHA
- Choline
- Lutein
- Iron
- Phospholipids (PLs)
  - PLs includes;
    - Sphingomyelin (SM),
    - Phosphatidylethanolamine (PE),
    - Phosphatidylcholine (PC),
    - Phosphatidylinositol (PI) and
    - Phosphatidylserine (PS)}

Macronutrients
Protein[a]
Specific fats (eg, LC-PUFAs)[a]
Glucose
Micronutrients
Zinc[a]
Copper[a]
Iodine[a]
Iron[a]
Selenium
Vitamins and cofactors
B vitamins (B_6, B_{12})
Vitamin A
Vitamin K
Folate[a]
Choline[a]

LC-PUFA, long-chain polyunsaturated fatty acid. Reprinted with permission from Georgieff MK, Brunette KE, Tran PV. Early life nutrition and neural plasticity. *Dev Psychopathol*. 2015;27(2):415.

[a] Nutrients that meet the principles for demonstrating a critical or sensitive period during development.

Nutrients that influence brain development & functions

Brain connectivity types and levels

Myelination

Nature (genetics)

Neurons

Nurture (environment/ experience)

Breast Milk & Physiological Benefits

Breastfeeding is associated with:

- Less risk respiratory and gastrointestinal infections
- Less risk for obesity and diabetes
- Less risk for allergies, possibly
- Optimal brain and cognitive development

What are the specific breast milk components that provide the observed benefits?

1. Victora et al., 2016, Lancet; Deoni et al., Neuroimaging, 2018

Phospholipids - human milk

In HM fat accounts for ~50% of the total energy contribution, of which 0.2–2.0% are PLs[1, 2]

- There are 5 major PLs;
  - 3 predominant PLs (62–80%)[1]
  - Phosphatidylethanolamine (PE)
  - Phosphatidylcholine (PC)
  - Sphingomyelin (SM) a sphingolipid
- 2 minor PLs (12–15%)[2-4]
  - Phosphatidylinositol (PI)
  - Phosphatidylserine (PS)

1. Jansson et al., 1981
2. Bitman et al., 1984
3. Braun et al., 2010
4. Garcia et al., 2012

Brain Lipids

- Among the body organs, the brain is one of the richest in lipids

Water (77-78%)

Lipids (10-12%)

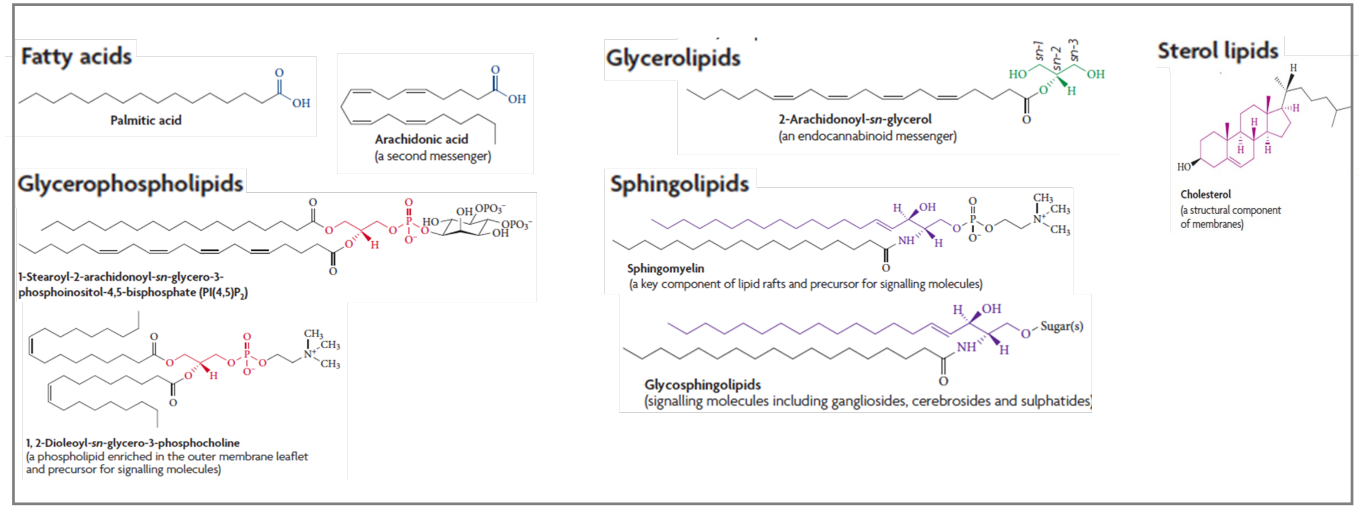
Protein (8%)

Carbohydrate (2%)

Soluble Inorganics (2%)

Inorganic Salts (1%)

Brain Lipids = ~ 100'000 different molecular species, e.g.



Piomelli et al. Nat Rev. Neurosc., 2007

Phospholipid - brain composition

	10 Months			6-yr old		
	Gray matter	White matter	Myelin	Gray matter	White matter	Myelin
Total Lipid	36.4	49	78	35.8	58.4	80.9
Total glycerophospholips	20.3	20.3	31.7	22.5	20.4	24.6
PE	6.8	9.4	14.2	10.6	8.6	11.3
PS	2.8	2.4	5.5	3.6	3.5	4.2
PC	10.8	8.6	12.1	8.3	8.3	9.1
Total sphingolipid	5.1	14.3	24.7	3.8	19.2	28.6
SM	1.8	2.1	4.6	1.3	2.7	4.4

Values are expressed as percentage of brain dry weight

Phospholipids – brain composition

- PLs are major components in the brain where they influence (1-3);
  - Structural membranes integrity
  - Metabolic pathways related to energetic homeostasis of the cells
  - Intracellular signaling processes / connections

1. Harris et al., 2005
2. Veloso et al., 2011; 3. FAO 2010

Myelination

The composition of white matter changes throughout development along with the composition of myelin

- Increasing presence of myelin / decrease in overall brain water content from birth to adulthood:
  from 87% in unmyelinated neonatal white matter to 72% in mature myelinated adult white matter[1,2]
- Increase in total lipid content
- Changes of the myelin composition itself

Constituent	2 Months	1 Year	5 Years
Protein	30	39	55.3
Total Lipids	29.5	49.6	58.2
Cholesterol	26.4	25	24.4
Phospholipid	66.1	53.4	49.8
Glycolipids	7.5	21.6	25.8

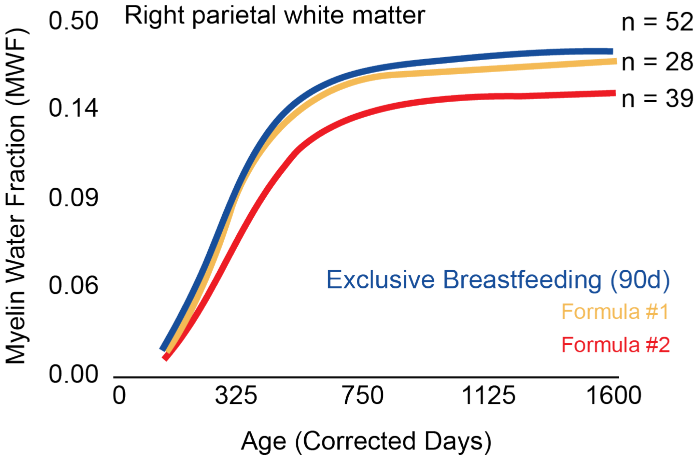
Table 1. Lipid composition of the brain throughout childhood development. The total lipid value is expressed as percent dry weight, all others in percent total lipid weight.

1. Samorajski and Rolsten, 1973
2. Morell et al., 1999

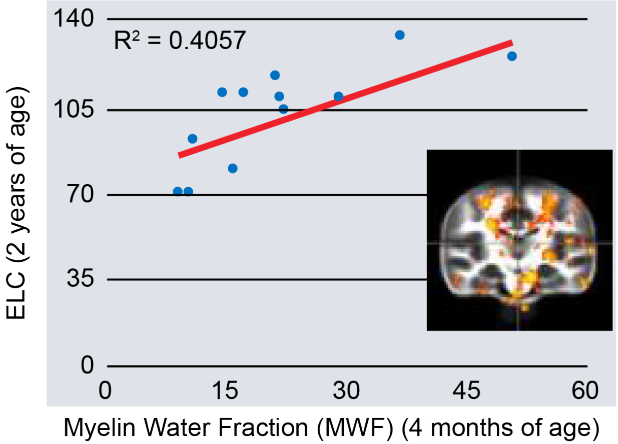
Interplay between Structural Functional Development and Nutrition

Scientific Hypothesis: Certain ingredients in infant nutrition support *de novo* myelination and subsequent cognitive development & learning

Nutritional Sensitivity

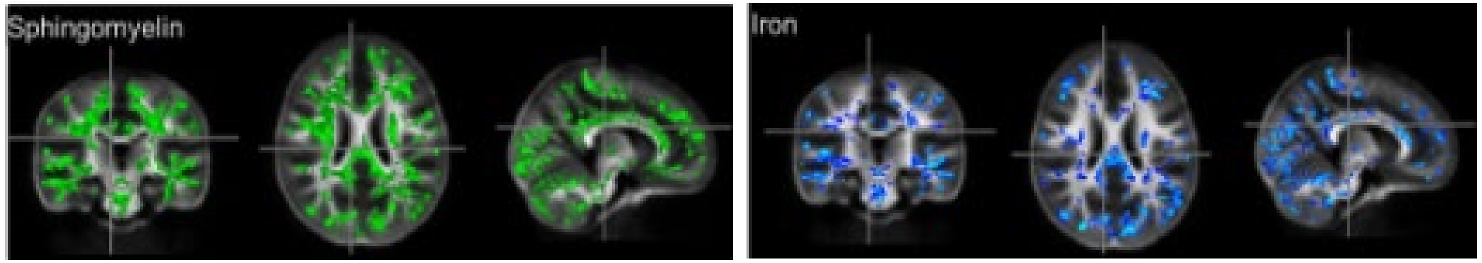


Predictability



Lipids

Pro-Myelin Nutrients: Sphingomyelin, DHA/ARA, Choline, Folic, Acid Iron



Association between sphingomyelin/iron and myelin in 0 - 5 year old children (S. Deoni, 2015)

Nora Schneider - Sean Deoni

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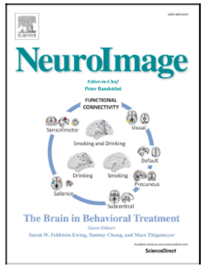
Lipids Promote Cognitive Development

Scientific Hypothesis: Certain ingredients in infant nutrition support *de novo* myelination and subsequent cognitive development & learning

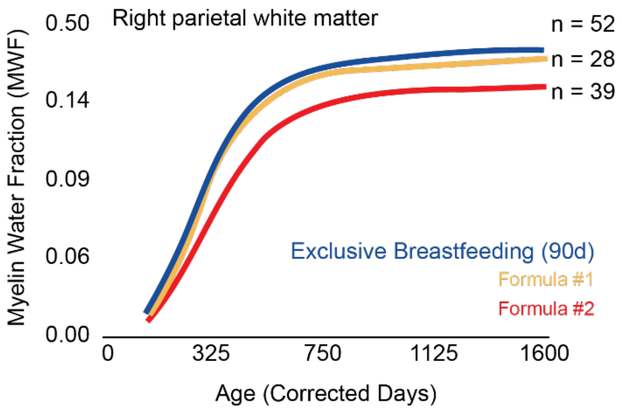


Early Nutrition Influences Developmental Myelination and Cognition in Infants and Young Children

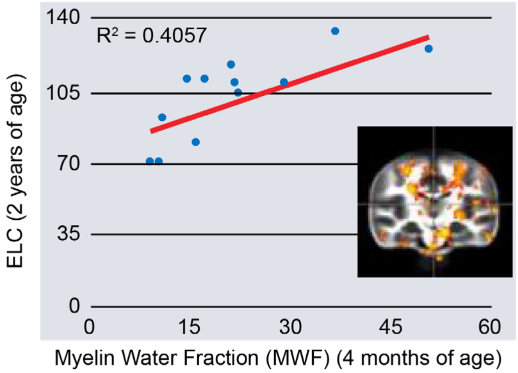
Sean Deoni** , Douglas Dean, Sarah Joelson, Jonathan O'Regan and **Nora Schneider

Modeling of myelin development in first 5 yrs of life & Measurable brain marker for myelination. S. Deoni personal communication

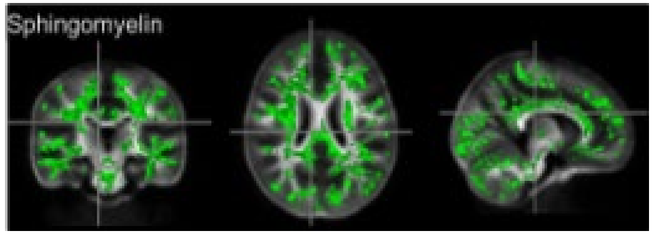
Nutritional Sensitivity



Predictability



Pro-Myelin Nutrient: Sphingomyelin



Association between sphingomyelin and myelin in 0 - 5 year old children (S. Deoni, 2015)

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Nora Schneider

Examples for Scientific Data

Deoni S, Dean III D, Joelson S, O'Regan J, Schneider N. Early Nutrition Influences Developmental Myelination and Cognition in Infants and Young Children. Neuroimage. 2017

Objective

- To examine longitudinal trajectories of brain and cognitive development in children who were exclusively breastfed versus formula-fed for at least 3 months
- To examine development between children who received different formula compositions

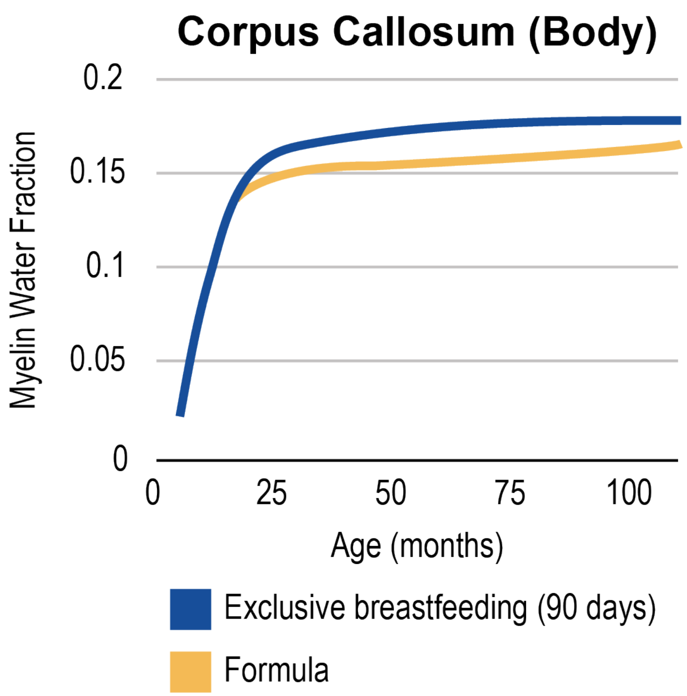
Population

- N = 62 breast-fed & N = 88 formula-fed infants

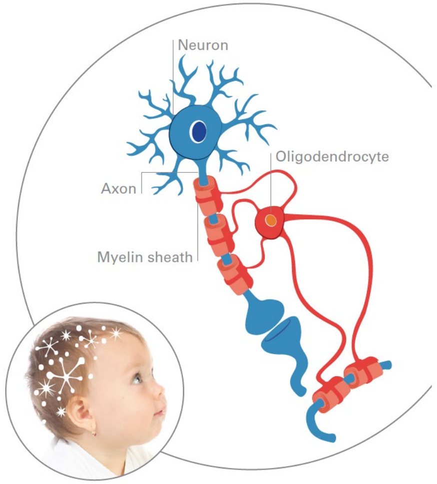
Results

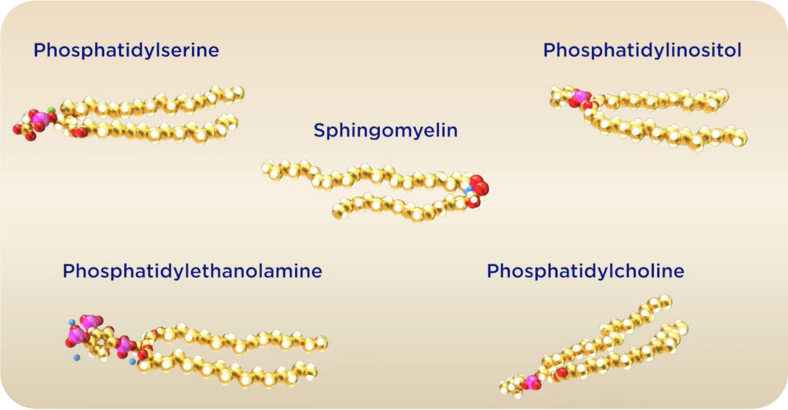
- Exclusively breast-fed infants had significantly improved myelination as well as higher cognitive scores (within normal ranges) compared to exclusively formula-fed infants.
- Retrospective analyses of individual nutrients showed significant associations with myelin content for DHA, ARA, folic acid, **sphingomyelin**, iron, and **phosphatidylcholine**

→ This observational data provides correlations, but no conclusions on supplementation effects



Polar Lipids





Structure & Function of Polar Lipids

- Structural components of neural tissues (Cell/ Membrane)
- Cell outgrowth and morphology
- Metabolism
- Synaptogenesis and synaptic transmission
- Myelination
  - Myelin biogenesis
  - Axon-glia communication
  - Long-term maintenance of myelin
- Peak rate of accretion overlaps with neurodevelopmental milestones

Brain Connectivity for fast & efficient brain communication

1. Schmitt et al. Biochemica et Biophysica Acta, 2015; 2. O'Brian et al. Journal of Lipid Reasearch, 1965

Sphingomyelin (SM)

- SM is particularly rich in the myelin sheath of the central nervous[1,2]
- SM is important for myelin integrity and function[3] & supports axonal maturation[4]
- SM and PC are the most abundant phospholipids in human milk fat[5,7]
- Breastfeeding provides the ideal form of nutrition for infants, and human milk is the only source of nutrients for exclusively breast-fed infants
- The average content of phospholipids in human milk ranges from approx. 9.8 to 47.4 mg/ 100 mL[5]
- It can be estimated that a 4 week old breastfed infant has a daily intake of 140 mg phospholipids per day[6] (at a concentration of 23.8 mg phospholipids/100 mL milk[7] and a consumption of 600 mL human milk at that age[8])
- SM and PL can be *de novo* synthesized

TABLE 6. Phospholipid and ganglioside composition of milk secreted for female and male infants, along with combined data

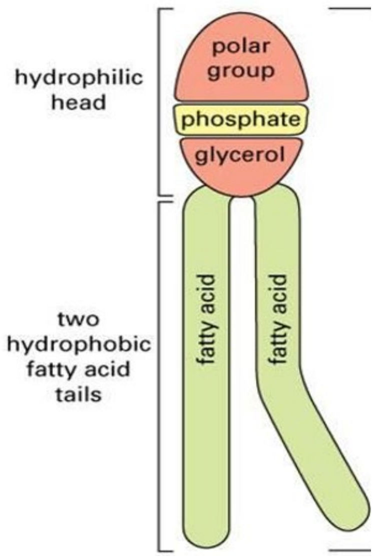
		Milk secreted forfemale infants		Milk secreted formale infants		Combined data		Gender contrasts (male vs. female)		
Variable (unit)	Visit (days)	Mean[a]	SD	Mean	SD	Mean	SD	Estimate	SE	*P*-value
Sphingomyelin (mg/100 ml)	30	8.07	1.32	8.86	1.99	8.47	1.72	0.85	0.69	0.223
	60	6.93	2.42	8.49	3.37	7.71	3.01	1.46	0.67	0.030
	120	7.89	2.72	9.37	2.40	8.66	2.64	1.64	0.66	0.013
Phosphatidylcholine (mg/100 ml)	30	5.81	1.26	6.12	1.42	5.97	1.34	0.33	0.50	0.507
	60	4.43	1.89	5.25	2.17	4.84	2.06	0.79	0.48	0.073
	120	4.52	1.98	5.32	1.72	4.94	1.88	0.90	0.47	0.059
Phosphatidylethanolamine (mg/100 ml)	30	6.47	1.62	7.05	2.06	6.76	1.86	0.62	0.76	0.415
	60	5.70	2.30	7.02	3.68	6.36	3.11	1.22	0.74	0.098
	120	7.24	3.23	8.85	2.81	8.08	3.10	1.76	0.72	0.015
Phosphatidylinositol (mg/100 ml)	30	0.99	0.27	1.15	0.41	1.07	0.35	0.16	0.15	0.283
	60	1.00	0.38	1.27	0.66	1.13	0.55	0.25	0.14	0.084
	120	1.51	0.66	1.81	0.63	1.67	0.66	0.35	0.14	0.012
Phosphatidylserine (mg/100 ml)	30	0.66	0.14	0.85	0.39	0.75	0.31	0.19	0.09	0.038
	60	0.70	0.30	0.80	0.35	0.75	0.33	0.09	0.09	0.296
	120	0.86	0.37	0.94	0.29	0.91	0.33	0.09	0.09	0.296
Total phospholipids (mg/100 ml)	30	22.01	4.41	24.03	5.42	23.02	4.88	2.15	2.05	0.294
	60	18.73	6.67	22.83	9.76	20.78	8.53	3.82	1.98	0.053
	120	22.02	8.63	26.29	7.44	24.24	8.23	4.75	1.95	0.015
GD3 (mg/100 ml)	30	0.23	0.16	0.23	0.08	0.23	0.12	−0.01	0.05	0.862
	60	0.20	0.26	0.17	0.10	0.19	0.20	−0.02	0.05	0.674
	120	0.13	0.17	0.20	0.21	0.17	0.19	0.06	0.05	0.252
GM3 (mg/100 ml)	30	0.25	0.09	0.22	0.07	0.23	0.08	−0.03	0.04	0.396
	60	0.27	0.12	0.30	0.15	0.29	0.14	0.04	0.04	0.277
	120	0.35	0.16	0.43	0.20	0.39	0.18	0.08	0.04	0.039

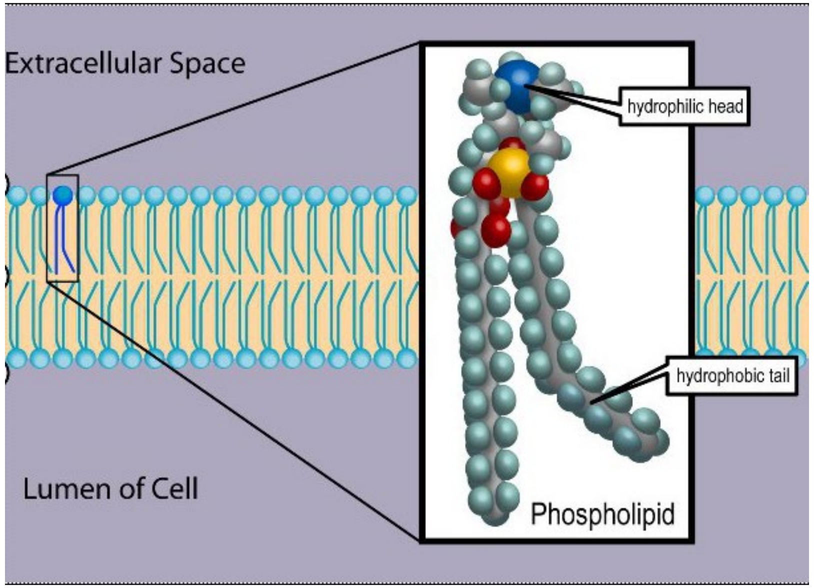
Gender contrasts along with *P*-values are also stated.
[a]Values are mean of 25 samples for individual genders and mean of 50 for combined data at each time point indicated.

1. Morell, 2012; 2. Spiegel I and Peles E, 2002; 3. Don et al. 2014; 4. Ledesma, 1999; 5. Cilla A. et al. Critical reviews in food science and nutrition, 2016; 6. Giuffrida F et al, Lipids, 2013 ; 7. Thakkar S et al. American Journal of Human Biology, 2013, 8. da Costa TH et al. Journal of Nutrition, 2010

Phospholipids - characteristics

Phospholipids structure





The polar group could be:

- Choline (PC)
- Inositol (PI)
- Serine (PS)
- Ethanolamine (PE)

Sphingomyelin sphingolipid

- Contains Sphingosine backbone

- Due to their hydrophilic and hydrophobic nature they play an important role in cell membranes
- They are found in high levels in the dendrites, myelin sheath and synapses neural structures that are vital for brain connections

1. Kullenberg et al., 2012; 2. Contarini & Povolo 2013; 3. Jansson et al., 1981; 4. Cilla et al., 2016; O'Brien & Sampson 1965; Hitzemann & Johnson 1983; Niebylski & Salem 1994; Slater et al., 1994; Zerouga et al., 1995; Horrobin DF. 1999; Harzer et al., 1983

Phospholipids and myelination

Pre-clinical data in rats:

- Pups were divided to 3 groups, 2 of which were treated with an inhibitor to SM *de novo synthesis*, L-Cycloserine (LCS), and 1 was normal
  - Then they were given a diet that was either supplemented with SM or a control diet (normal pups received diet without SM)
- Feeding pups diet supplemented with sphingomyelin resulted in;
  - Higher levels of brain weight, myelin dry weight and myelin total lipid content as compared to un-supplemented group who had significantly lower levels
  - SM supplementation had outcomes similar to normal pups

Oshida et al., 2003

Phospholipids and myelination

Pre-clinical data in rats :

Table 1. *Effects of dietary sphingomyelin on brain and myelin weights and myelin lipids**

	Experimental group		
	Non-LCS	LCS	SM-LCS
Brain wet wt (g)	1.67 ± 0.01[a]	1.55 ± 0.01[b]	1.64 ± 0.01[a]
Myelin dry wt (mg/brain)	24.4 ± 0.5[a]	12.9 ± 0.5[b]	21.7 ± 0.8[c]
Myelin total lipid content (mg/brain)	17.2 ± 0.5[a]	8.5 ± 0.2[b]	14.8 ± 0.4[c]

Values are mean ± SEM (n = 6)

*Values with different letters are significantly different at $p < 0.05$

1. Oshida et al., 2003

Phospholipids and myelination

- A pilot clinical study
- Objective: examine the effects of sphingomyelin (SM), on the mental, motor and behavioral development of premature infants
- Design: Randomized, controlled and double blinded pilot study
- Subjects: 24 very low birth weight (<1500g) premature infants who were predominantly breastfed, and shortage was covered with either milk fortified with SM or control. They were followed up to 18 months
- Study arms:

- Control group - SM 13% of all phospholipids in milk n =12	**- SM-fortified group - 20% of all phospholipids in milk n = 12**

- Outcomes measured:
  - Mental, motor and behavioral development

Tanaka et al., 2013

Phospholipids and myelination

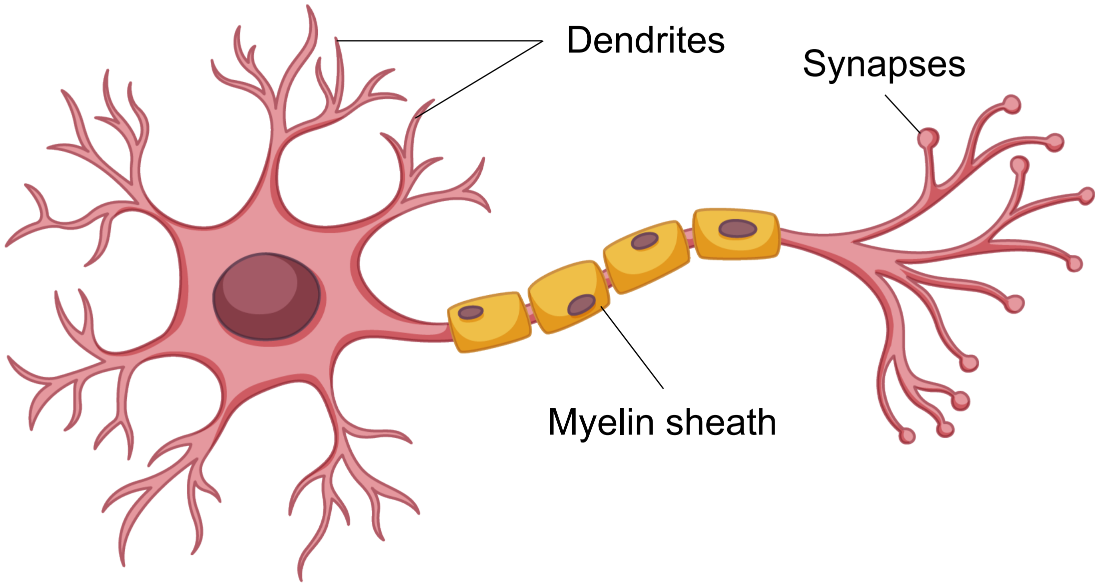
Results

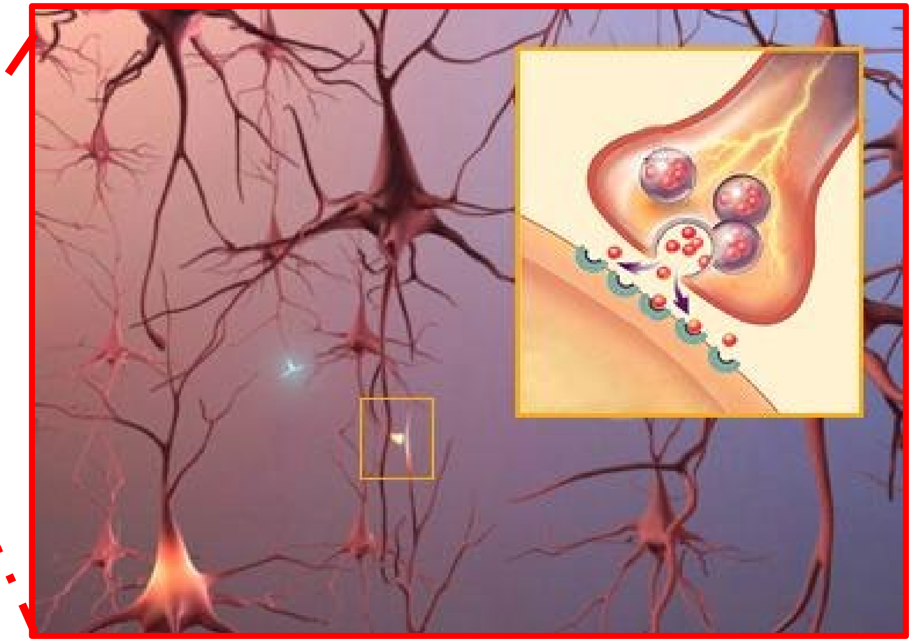
- The percentage of SM in the total phospholipids in red blood cells was significantly higher in the SM-fortified group than in the control
- The Behavior, cognition, and visual test results at 18 months were significantly better in the SM-fortified group than in the control

Authors conclusion: In very low birth weight infants, nutritional intervention with SM-fortified milk has a positive association with the neurobehavioral development of these infants

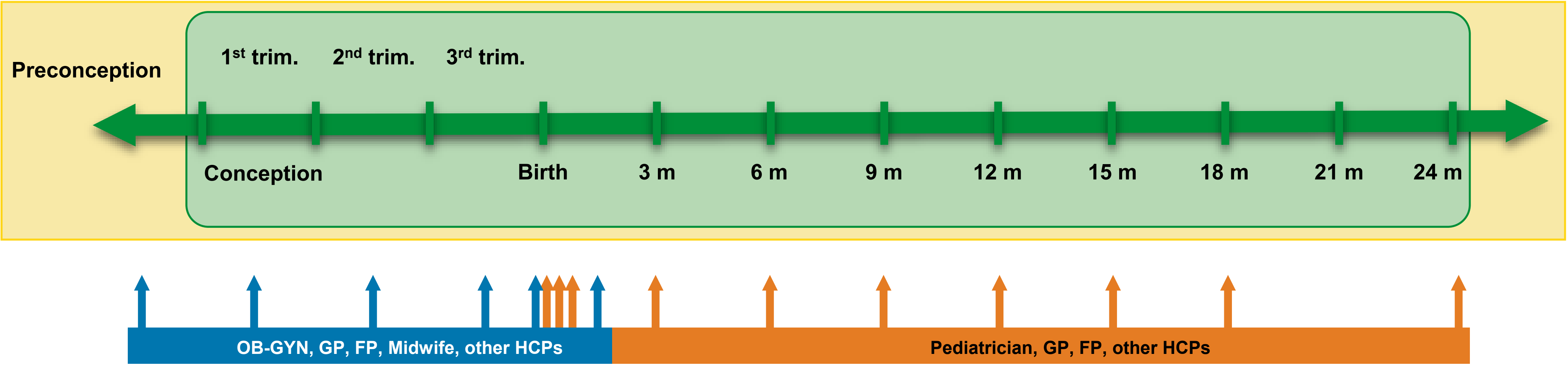
PLs and cell signaling - Brain Connection

- PLs are found in high levels in the dendrites, myelin sheath and synapses
- Their integrity and signaling function is high dependent on PLs





The privilege and responsibility to make a difference



Early childhood represents the sensitive window of growth and neurodevelopment

Physicians and other healthcare providers have multiple interactions with parents and children and have the opportunity to play a critical role in supporting optimal growth and developmental outcomes

The 1,000 Days Partnership. http://www.thousanddays.org/about/. Accessed June 19, 2012.

THANK YOU