Wyeth® Nutrition SCIENCE CENTER


# The Role of Polar lipids in brain & cognitive development

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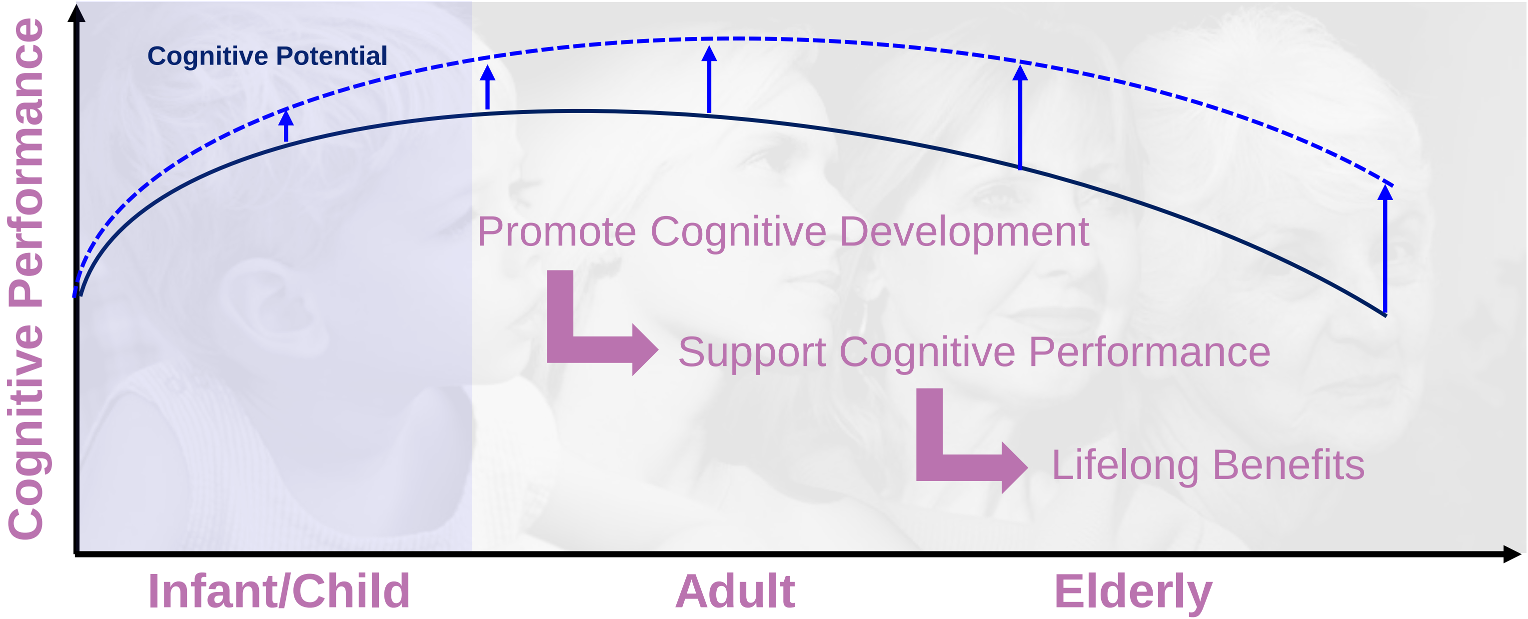
March 10, 2020

# Brain Development and Cognition

**Optimal brain development** is a foundation for a **prosperous** and **sustainable** society

*Center for the Developing Child, HARVARD UNIVERSITY*



# Presentation Outline

- Brain development and maturation
- Importance of myelin formation for cognition
- Role of polar lipids in brain and cognitive development

**Ramón y Cajal & the "neuron doctrine" (1891)**

(1a) The brain is composed of discrete individual signaling elements (neurons)

(1b) Information passes from neuron to neuron across gaps (synapses)

(2) Information is polarized

**Ramón y Cajal (1893–1894)**

(3) "It is feasible that mental exercise leads to increase growth of neuronal branches and cell junctions (synapse)"

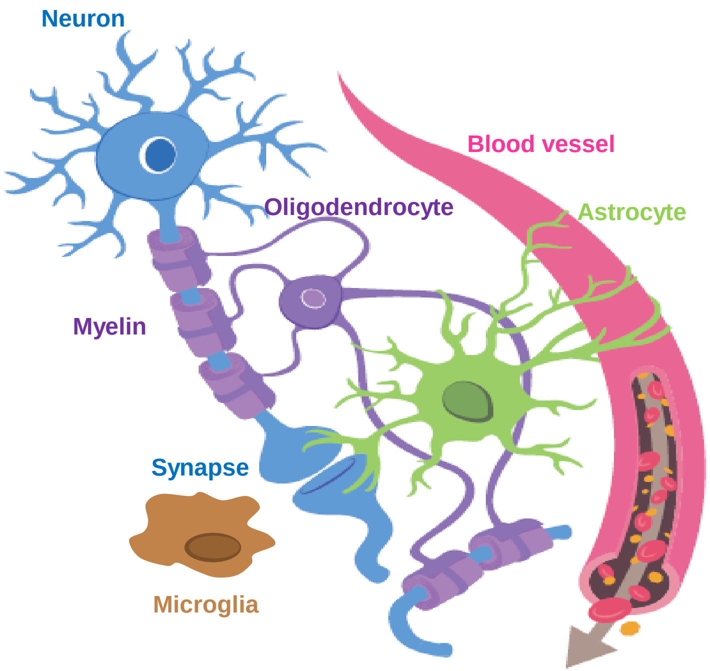
**STRUCTURE**

↕

**FUNCTION**

➡ **SYNAPTIC PLASTICITY**

# The brain is more than neurons



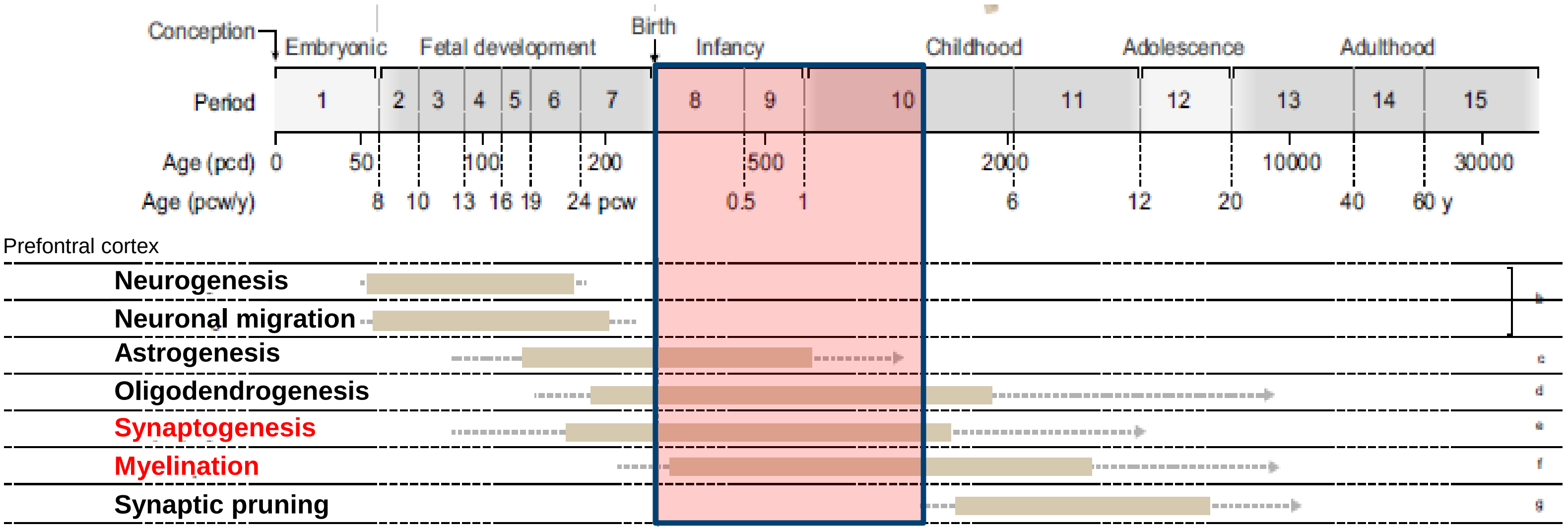

- **Neuron**: information transmission and processing
- **Astrocyte**: brain energy provider
  information transmission modulator
- **Microglia**: guardian of the brain
- **Oligodendrocyte**: information transmission facilitator
- **Endothelial cell / pericyte**: (blood vessels) filter/supplier

- **90 billion neurons (100,000,000,000)[3]**
- **100 billion non-neuron cells (100,000,000,000)**
- **1 quadrillion synapses (1,000,000,000,000,000)**
- **100 km of nerves**
- **600 km of blood vessels[3]**
- **Adult brain comprises 2% of total body weight but consumes 20% of total energy[4]**

.1. Leuret and Gratiolet, 1854; 2. Kasthuri N, et al. *Cell* 2015;162:648–681; 3. Wong A, et al. *Front Neuroengineering* 2013;6:1–22; 4. Ascoli G. *N Eng J Med* 2015;373:1170–2.

# How do we reach such complexity?

# Timeline of key human neurodevelopmental processes




*Adapted from Silbereis JC, et al., Neuron 2016;89:248–68*

- After birth, billions of neurons get connected by **synaptogenesis** : 700,000 synapses/second are formed
- **Myelination** develops rapidly to enhance neuron communication throughout the entire brain[1,2]
- → These **early experience-dependent** processes underlie the **plasticity & capacity for adaptation** that is the hallmark of early brain development[3]

pcd, post-conceptional days, pcw,/y post=conceptional weeks/years; y years.


1. Deoni S, et al. *Neuroimage* 2018;178: 649-59; 2. Hauser J. et al. *Nutritional Neuroscience*, 2019, In Press;

# Key factors influencing brain development

**General**[1]

**Gene expression** (nature)

**Environmental factors** (nurture)

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

**Environmental factors**[1]

Socioeconomic status

Social interactions

Urbanization

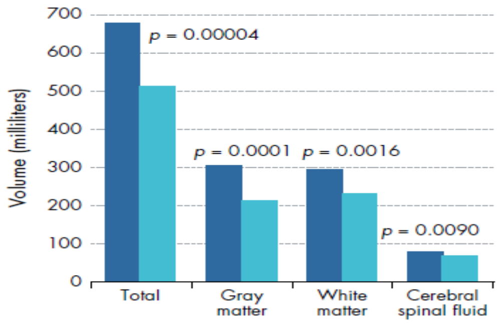
Pollution

Social mobility

Stress

Nutrition & food

**Total white and gray matter** (stunting status)




**Not malnourished**
n=18 (age 73 ± 8 days)

**Malnourished**
n=9 (age 82 ± 11 days)

*WDR team, 2018*[3].

SES, socioeconmic status.

1. Kolb B, Gibb R. *J Can Acad Adolesc Psychiatry*. 2011;20: 265-76; 2. Hanson JL, et al. Plos One 2013;8:e80954; 3. WDR team 2018, using data from Nelson and others (2017). Available here: http://bit.do/WDR2018-Fig_S2-1;

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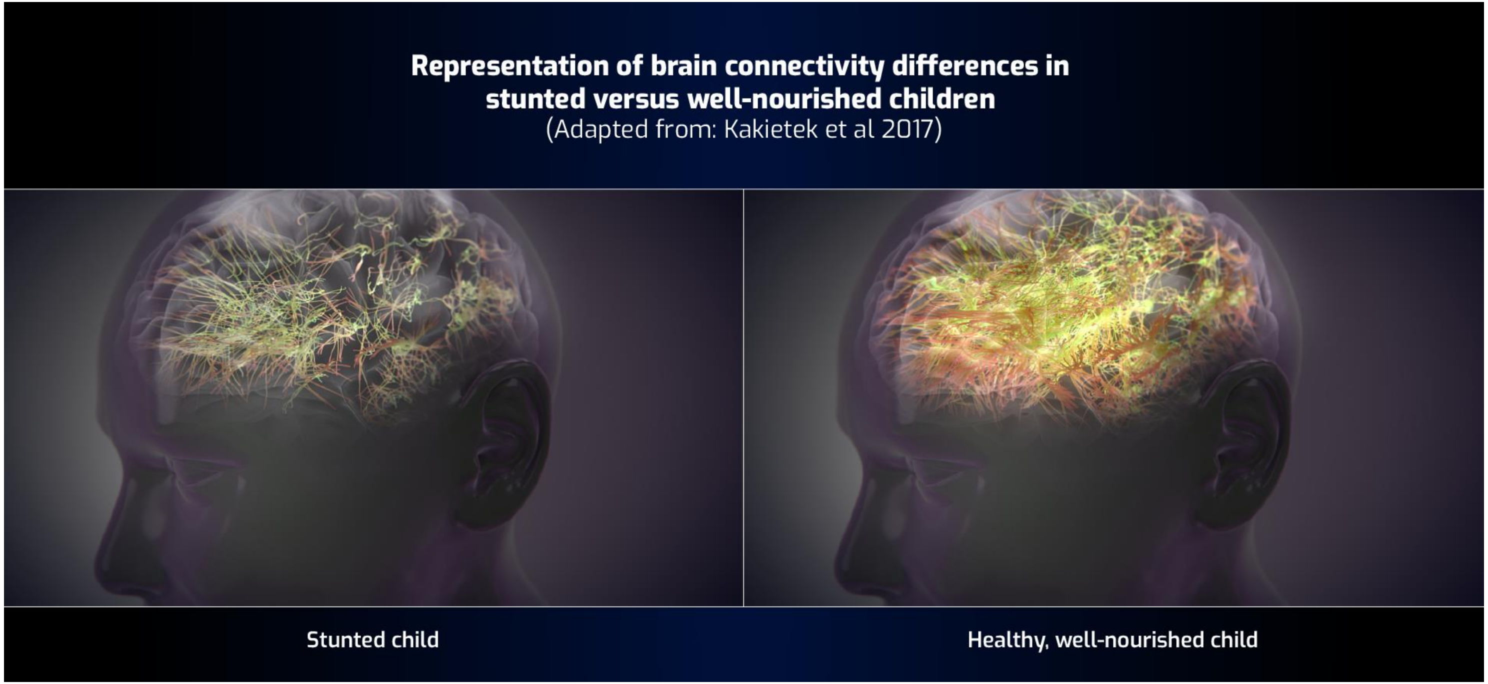
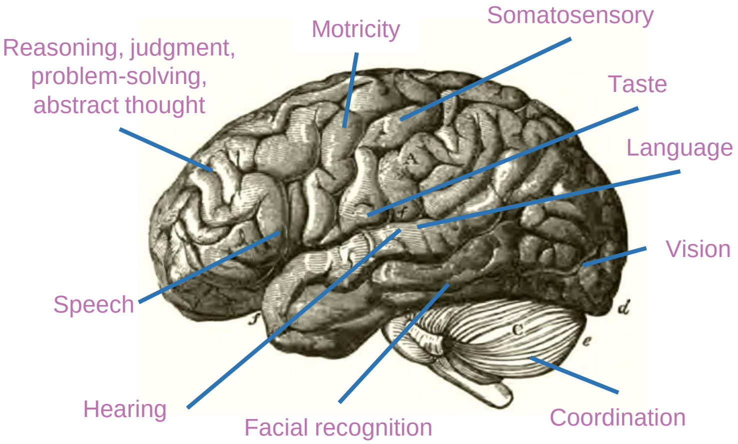
# Influencing Factors



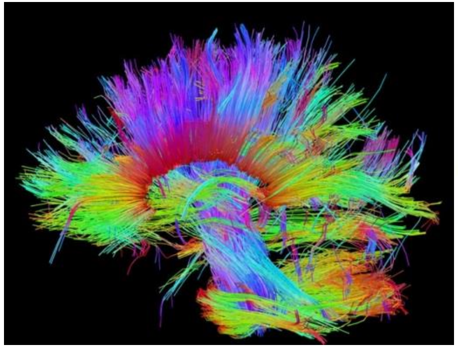

Nelson (2017); Kakietek et al 2017

# Brain has specialized areas & functional network to support cognitive tasks through information integration

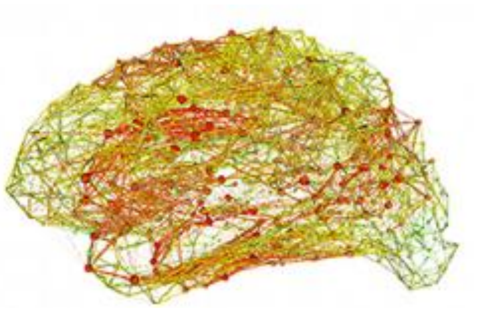



*Ackerman S, 1992*[1]

**Brain functional connectivity**



*Source: Human Connectome Project*[2]

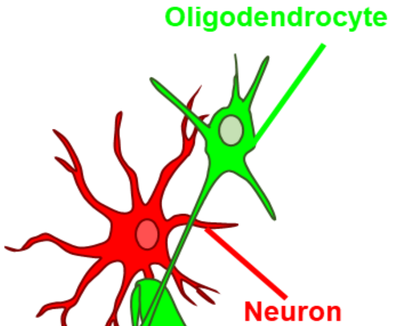
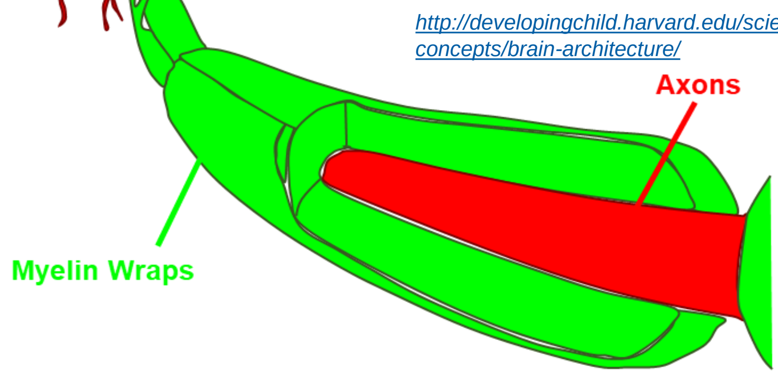


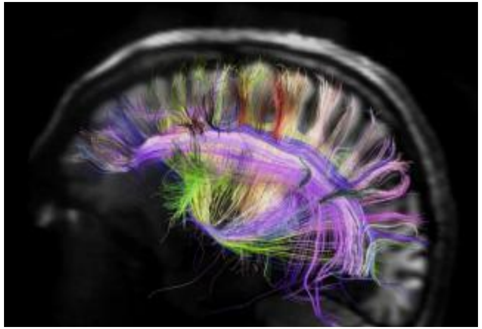
*van den Heuvel & Sooms, 2011*[3]

**Proper connectivity is key for proper brain and cognitive functions**

1. Ackerman S. Discovering the Brain. National Academies Press (US), 1992; 2. http://www.humanconnectomeproject.org/; 3. van den Heuvel MP, Sporns P. *J Neurosci* 2011; 31:15775–86

# Myelin: more rapid and efficient communication between neurons

http://developingchild.harvard.edu/science/key-concepts/brain-architecture/

- Myelin = insulator by increasing axonal resistance and decreasing capacitance[1]
- Myelin sheath thickness, affect the conduction velocity of action potentials[1]
- Velocity: unmeylinated axon: 5m/sec[1]
  meylinated axon: 100 m/sec[1]

Adapted from 1. Chang et al., Nature Neuroscience, 2016

# Benefits of myelination

Clinical studies show the link between myelination and cognition, including:[1-13]

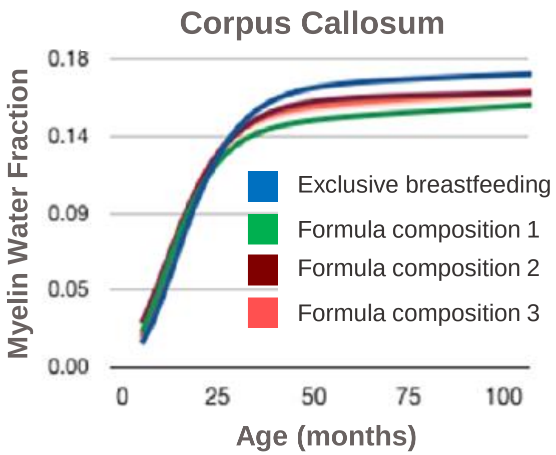

*Modeling of myelin development in first 5 years of life & measurable brain marker for myelination.*
*Deoni, S, personal communication*

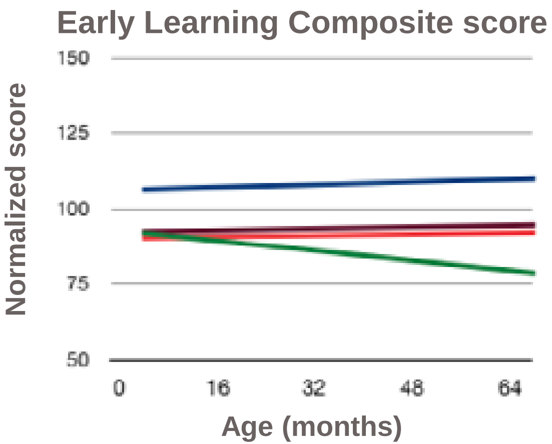
- general cognitive ability
- Language and reading
- EFs (working memory)
- processing speed
- sensory reactivity

1. Schmithorst V, et al. *Hum Brain Mapp* 2005;26:139–47; 2. Deoni S, et al. *Hum Brain Mapp* 2016;221:1189–203; 3. Büchel C, et al. *Cerebral Cortex* 2004;14:945–51; 4. Catani M, et al. *PNAS* 2007;104:17163–68; 5. O'Muircheartaigh J, et al. *Journal of Neuroscience* 2013;33:16170–77; 6. Nagy Z, et al. *J Cogn Neurosci* 2004; 16:1227–33; 7. Beaulieu C, et al. *Neuroimage* 2005; 25:1266–71; 8. Nagy, et al. 2004; 9. Short S, et al. *Neuroimage* 2013; 64:156-66;10 . Turken A, et al. Neuroimage 2008,42:1032–44 ; 11. Bartzokis G, et al. *Neurobiol Aging.* 2010;9:1554–62; 12. Lu, et al. *Brain Cogn* 2013;81:131–8; 13. Weinstein M, et al. *Neuropsychologia* 2014.; 62:209 –19

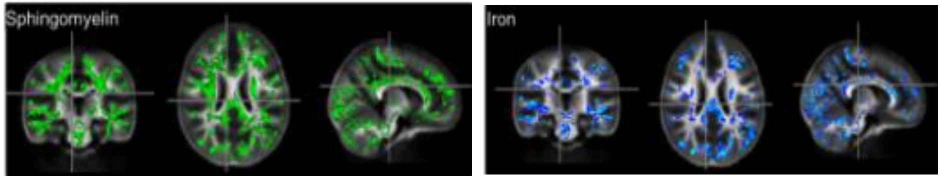
Original concept developed by Nora Schneider and Sean Deoni

# Interplay between structural functional development and nutrition




**Pro-Myelin Nutrients: Sphingomyelin, DHA/ARA, Choline, Vit B9, Vit B12, Iron**




*Association between sphingomyelin/iron and myelin in 0 - 5 year old children. S. Deoni, personal communication*

ARA, arachidonic acid; DHA, docosahexaenoic acid; MWF, myelin water fraction.

Deoni S, et al. *Neuroimage* 2018;178: 649-59

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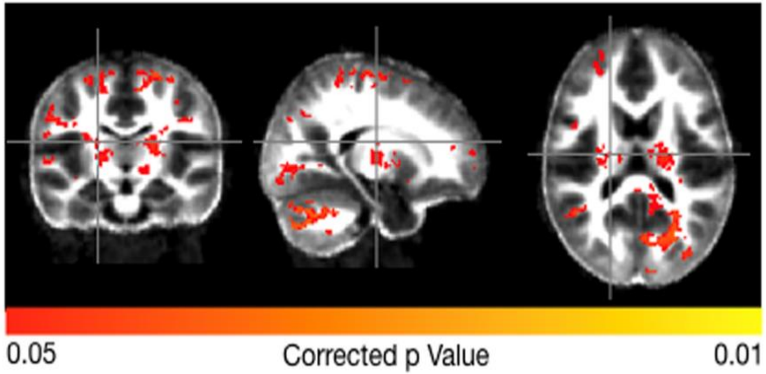
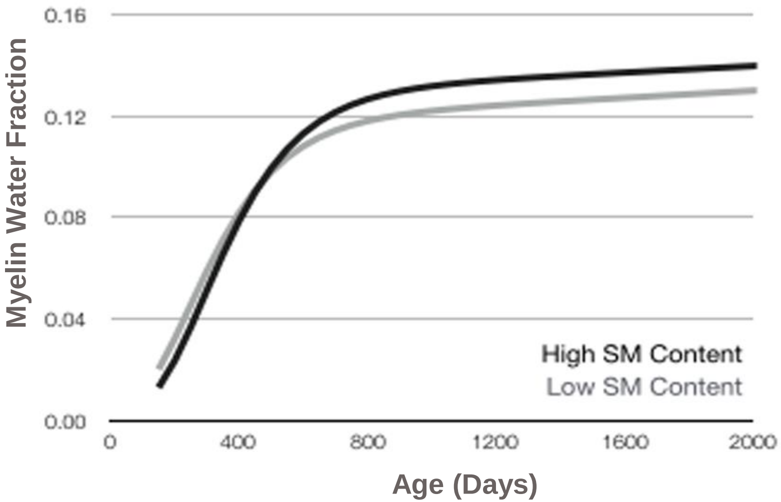
# Observational data shows positive associations between dietary sphingomyelin & myelination



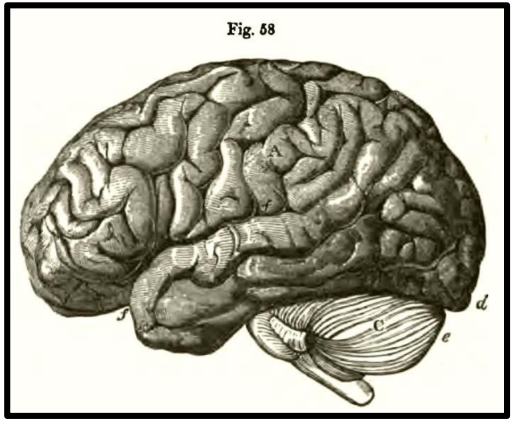




Brain regions with a significant relationship between dietary Sphingomyelin and myelin content (12 and 24 months of age).

White matter myelination trajectories for children who received a product composition with high SM content (71mg/L) versus a lower SM content (28mg/L).

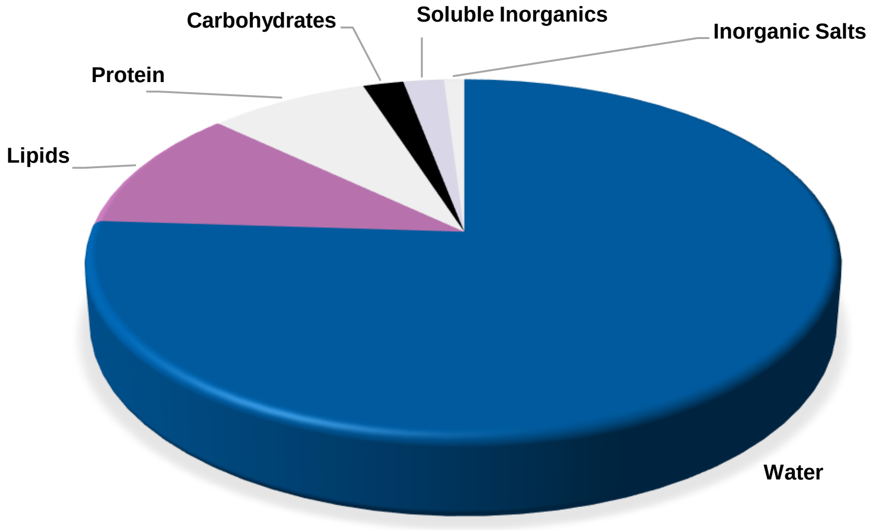
Schneider N., et al. *eNeuro. 2019 Aug 6;6(4)*

# The fattiest organ of the body



# 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%)

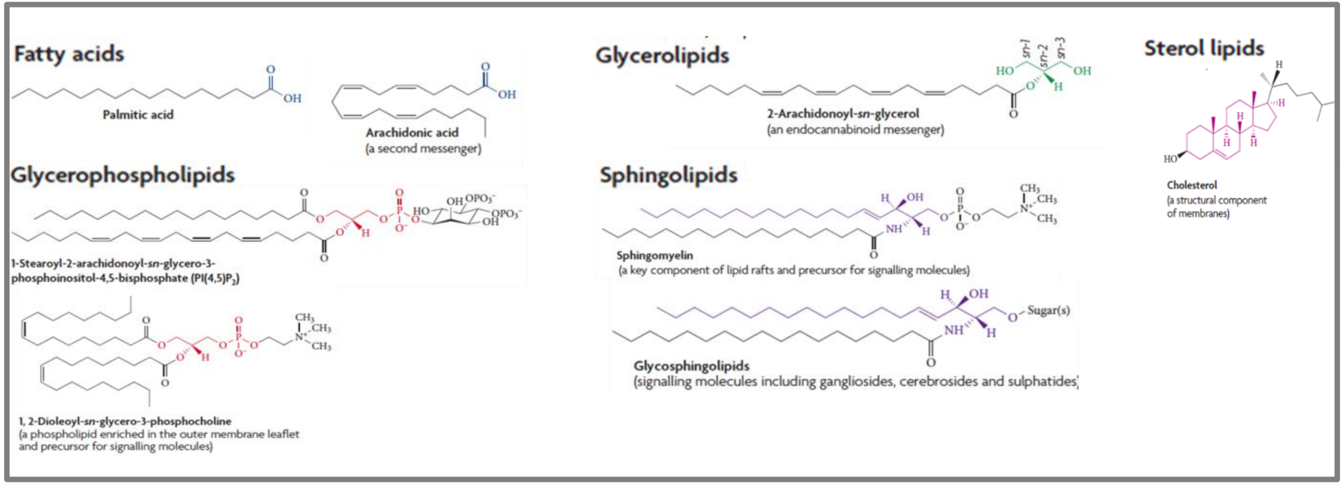
Inorganic Salts (1%)

***Piomelli et al. Nat Rev. Neurosc., 2007***

# Brain Lipids

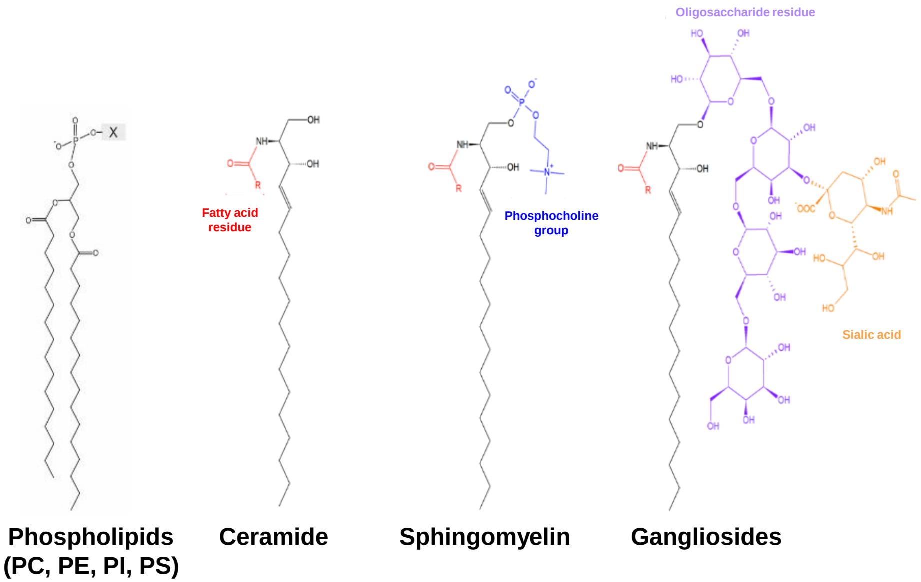
**Among the body organs, the brain is one of the richest in lipids**

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




*Piomelli et al. Nat Rev. Neurosc., 2007*

# Polar Lipids: Brain Building Blocks

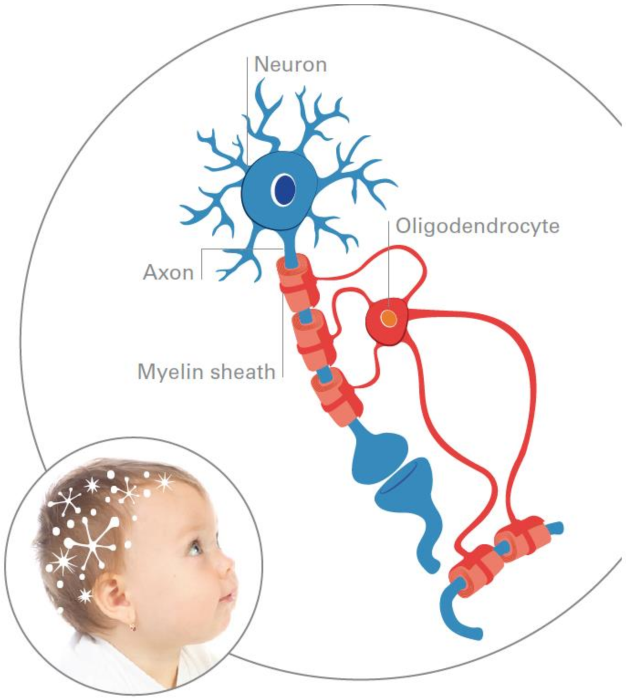



## Structure & Function of Polar Lipids

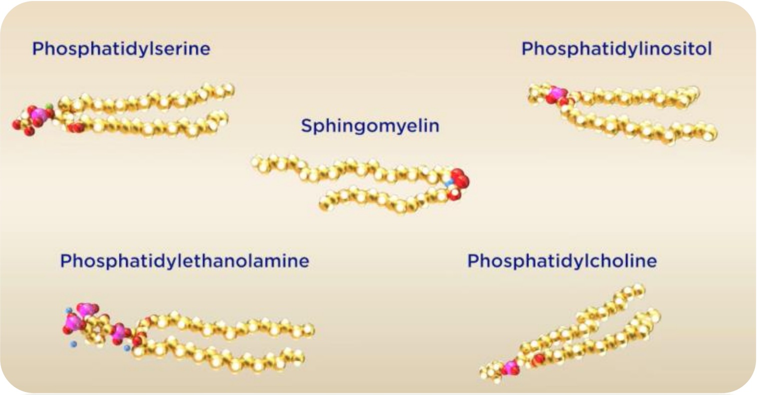
- Naturally present in Human Milk
- Structural components of neural tissues
- Neuronal outgrowth and morphology
- Energy Metabolism
- Synaptogenesis and synaptic transmission
- Myelination

**Brain Connectivity for fast & efficient brain communication**

# Myelin Lipids[1,2]




- Myelin sheaths are lipid-rich membrane stacks
- Overall ratio of proteins to lipids of around 1 to 186
- Most part of the lipids are **polar lipids**, including phospholipids and sphingomyelin

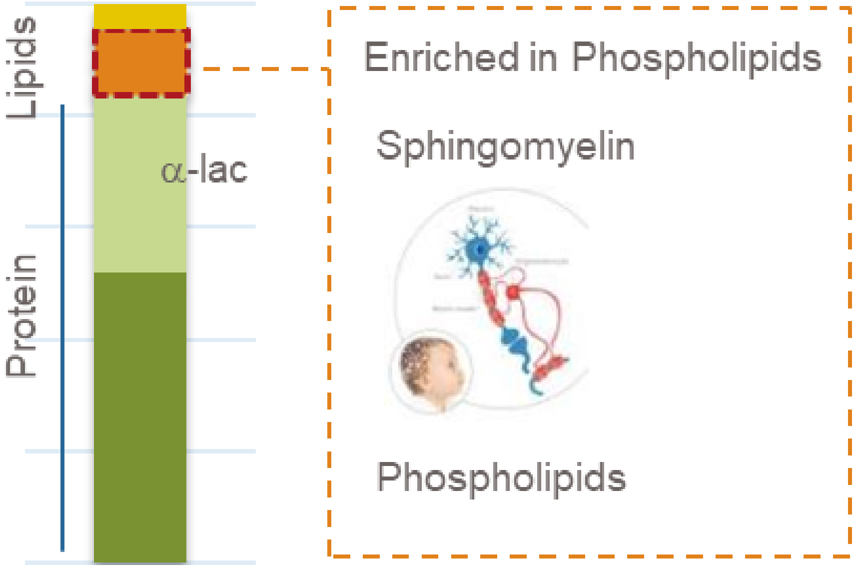



[1]Schmitt et al. Biochemica et Biophysica Acta, 2015; [2]O'Brian et al. Journal of Lipid Reasearch, 1965

# Sources of Polar Lipids in Infant Nutrition

α-lactalbumin[1,2]

- Major protein in human milk, rich in amino acids
- Improves protein composition when added to infant formula
- A rich source of polar lipids (e.g. Sphingomyelin) as it uses a specific process that retains polar lipids




[1]Moloney et al. 2018; [2]Zou et al. 2017

# Sources of Polar Lipids in Infant Nutrition

- SM is rich in the myelin sheath – important for myelin integrity, myelin function and supports axonal maturation[1]
- Sphingomyelin (SM) and Phosphatidylcholine (PC) are the most abundant phospholipids in human milk fat[1,2]
- SM and PL can be *de novo* synthesized

| Variable (unit) | Combined data Mean | Combined data SD |
|---|---|---|
| Sphingomyelin (mg/100 ml) | 8.47<br>7.71<br>8.66 | 1.72<br>3.01<br>2.64 |
| Phosphatidylcholine (mg/100 ml) | 5.97<br>4.84<br>4.94 | 1.34<br>2.06<br>1.88 |
| Phosphatidylethanolamine (mg/100 ml) | 6.76<br>6.36<br>8.08 | 1.86<br>3.11<br>3.10 |
| Phosphatidylinositol (mg/100 ml) | 1.07<br>1.13<br>1.67 | 0.35<br>0.55<br>0.66 |
| Phosphatidylserine (mg/100 ml) | 0.75<br>0.75<br>0.91 | 0.31<br>0.33<br>0.33 |
| Total phospholipids (mg/100 ml) | 23.02<br>20.78<br>24.24 | 4.88<br>8.53<br>8.23 |
| GD3 (mg/100 ml) | 0.23<br>0.19<br>0.17 | 0.12<br>0.20<br>0.19 |
| GM3 (mg/100 ml) | 0.23<br>0.29<br>0.39 | 0.08<br>0.14<br>0.18 |

[2]Thakkar et al 2013

[1]Zheng et al. 2019 Adv Nutr, [2]Thakkar et al 2013

# Wrap up & key messages

# Key messages

- The first years of life are a rapid & dynamic period for brain maturation
- Most brain processes during that period are primarily focused on connecting the brain, e.g. myelination
- Many factors influence brain growth and myelination; early life nutrition is an important and modifiable factor that can shape myelination and, consequently, cognitive outcomes
- Lipids play an important role in brain, myelin and cognitive development, particularly polar lipids e.g. phospholipids and sphingomyelin

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# Sources of Polar Lipids in Infant Nutrition

- Overall, milk phospholipids are important sources of components relevant for neurodevelopment (e.g. long-chain polyunsaturated fatty acids and choline)[1]
- Sources of phospholipids & polar lipids for infants are human milk & infant nutrition with differences in concentration and proportion in human milk[2]

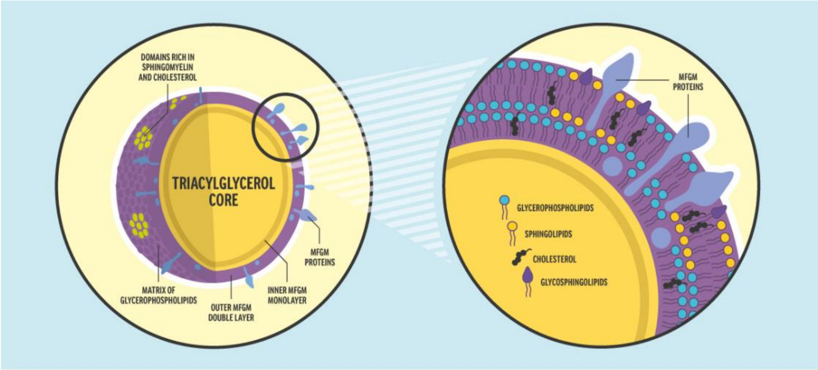

Figure 1: Milk Fat Globule (left) and zoom into the Milk Fat Globule Membrane layers (right)

*https://www.arlafoodsingredients.com/our-ingredients/pediatric-nutrition-ingredients/milk-fat-globule-membrane/*

**[1]Ingvordsen Lindahl et al. 2019; [2]Zheng et al. 2019;**

# Polar Lipids & Brain Development

**Preclinical data**

Dietary SM may contribute to myelination of the central nervous system in the early postnatal period in an induced myelination deficiency model in rats[1]

**Clinical findings**

A pilot study in low-birth-weight infants shows that SM-fortified infant formula results in some improved behavior rating scores, information processing and sustained attention at 18 months compared to the control group[2]

→ Underlying mechanism unknown, but improvements in myelination (via cerebrosides, sulfatides) or membrane fluidity (via sphingomyelins) speculated by the authors

**[1]Oshida et. al., 2003; [2]Tanaka et. al., 2013**