

# SPHINGOMYELIN & ITS ROLE IN COGNITION

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# Objectives

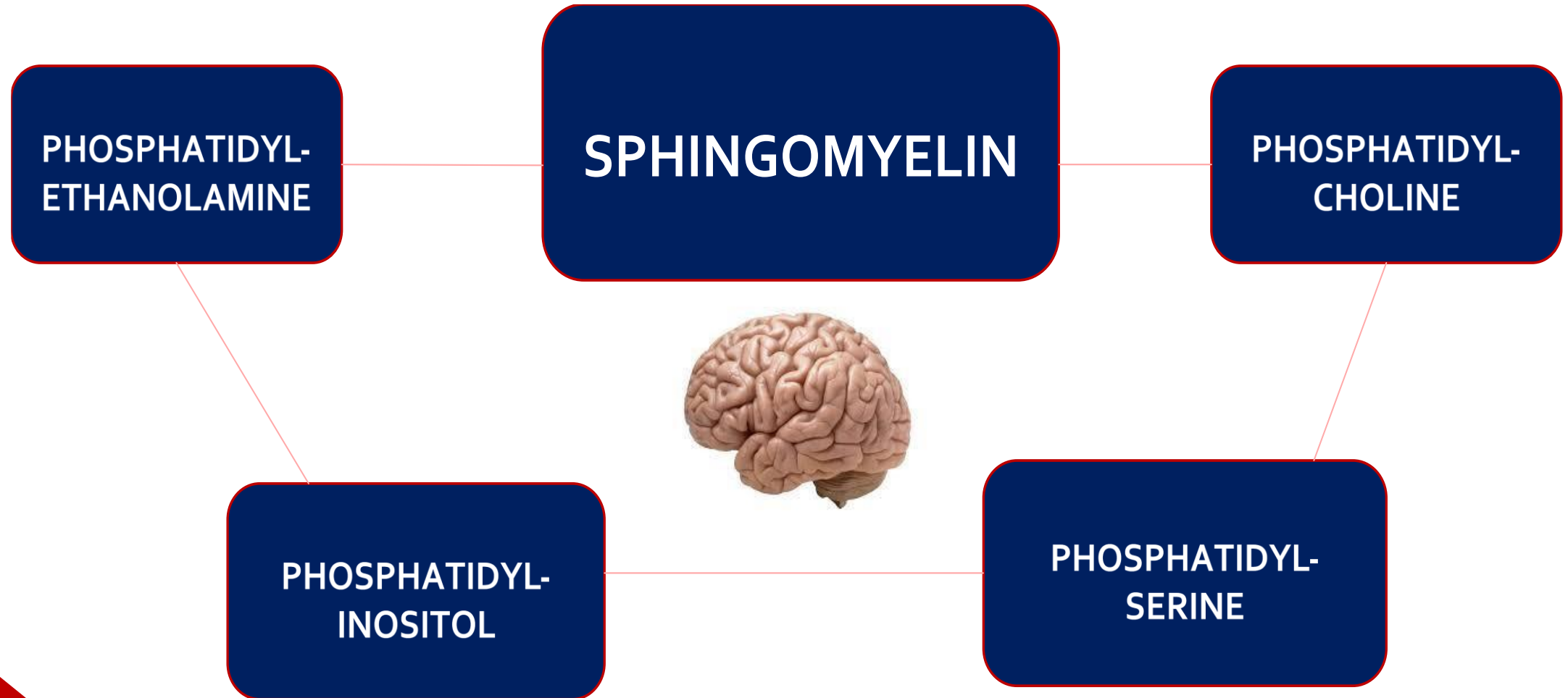
Participants are expected to:

- To recognize infancy & early childhood as critical windows of opportunity for brain growth and normal child development
- To appreciate the role of Sphingomyelin in development of cognitive functions in children.
- To appreciate the role of proper infant feeding/ nutrition in development of Cognition.

# *THE BRAIN PHOSPHOLIPIDS*

The nervous system is among the tissues of the mammalian body with the highest lipid content, as well as the highest lipid complexity

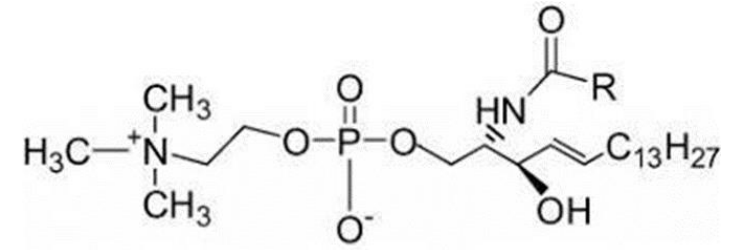
# There are 5 major Phospholipids in the Brain



# SOURCES OF BRAIN LIPIDS

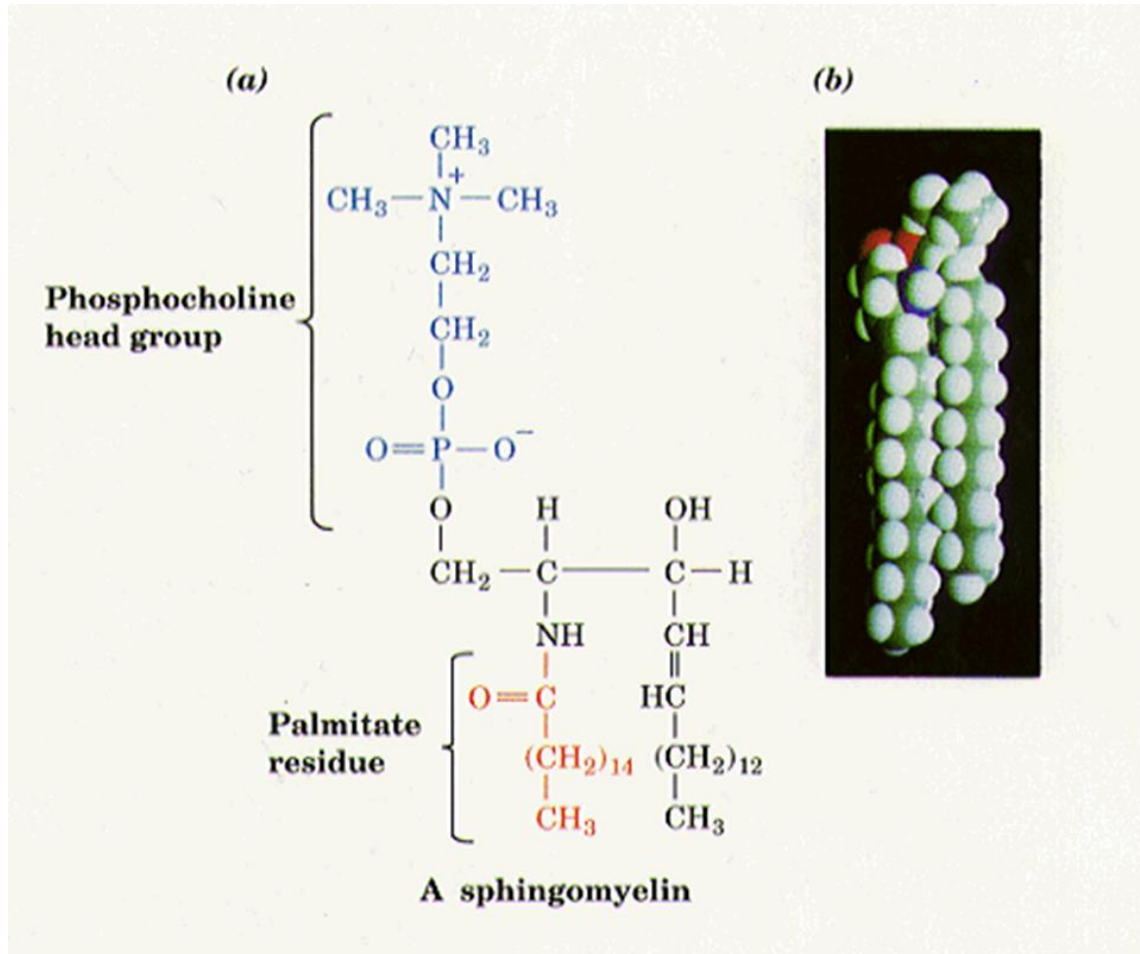
- Overall, milk phospholipids are important sources of components relevant for neurodevelopment (e.g. long-chain polyunsaturated fatty acids and choline) <sup>1</sup>
- Sources of phospholipids & polar lipids for infants are human milk & infant nutrition with differences in concentration and proportion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

# Sphingomyelin (SM) - a structural building block of the brain



- The most abundant phospholipid in human milk
- By age 4 weeks, SM accounts for 35% of phospholipids in human milk.

SM levels in the brain increase from 2% at birth to 15% at 3 years  
The increase is consistent with a progressive increase in neuronal myelination after birth



# STRUCTURE OF SPHINGOMYELIN

# FUNCTIONS OF SPHINGOMYELIN

- Neurogenesis
  - Via axonal spouting
  - Axonal branching
- Synaptogenesis
  - Synaptogenesis & Synaptic transmission
  - Modulates postsynaptic balance ratio of SM/Ceramide
- Myelination



- Regulator of cellular events by its ability to form microdomains in the plasma membrane

# Sphingomyelin & Axonal Growth

- Axonal outgrowth,
  - projection of the axon from the soma of a neuron towards a target cell,
  - is an essential process in the wiring of the neural network.
  - It has been shown that inhibition of CERS activity leading to depletion of ceramide, SM and GSLs significantly reduces axonal outgrowth and axonal branching in cultured hippocampal neuron.
  
- Hatel R, Futerman AH

# Sphingomyelin & Synaptic Plasticity

- Sphingolipids play an important role in organizing neuronal membranes,
  - Alterations in the sphingolipid pathway have been associated with disturbances in neuronal plasticity.
  - Synaptic plasticity covers several phenomena including long-term potentiation (LTP),
  - LTP is strengthening of synapse signalling through repeated presynaptic stimulation.
  - LTP is one of the major mechanisms constituting the basis for memory and learning.
- Hatel R, Futerman AH

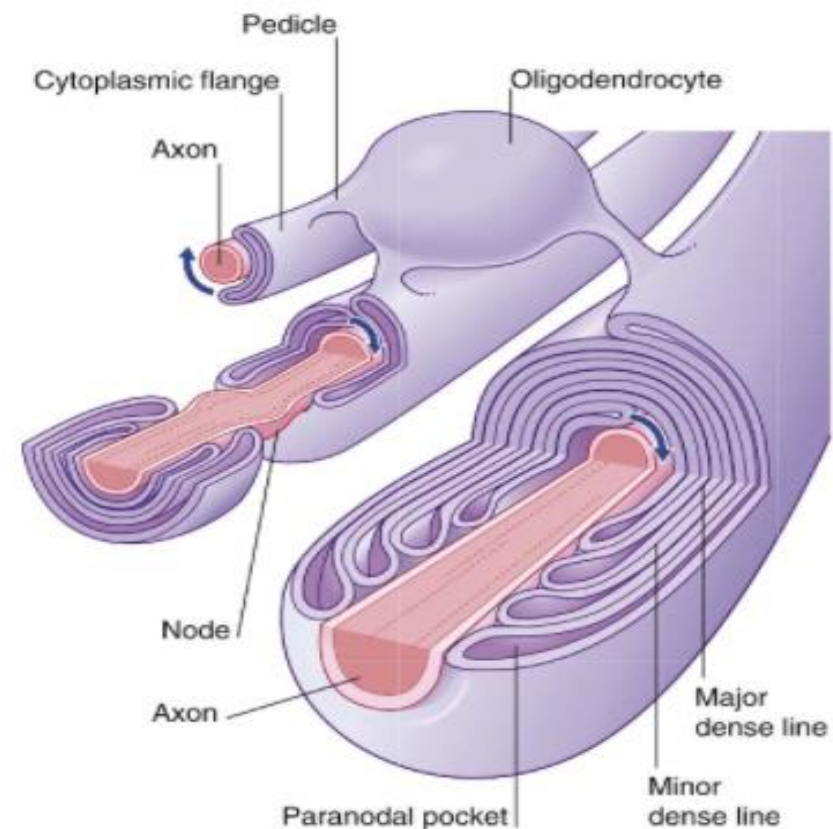
# Learning

A process of creating and strengthening frequently used synapses

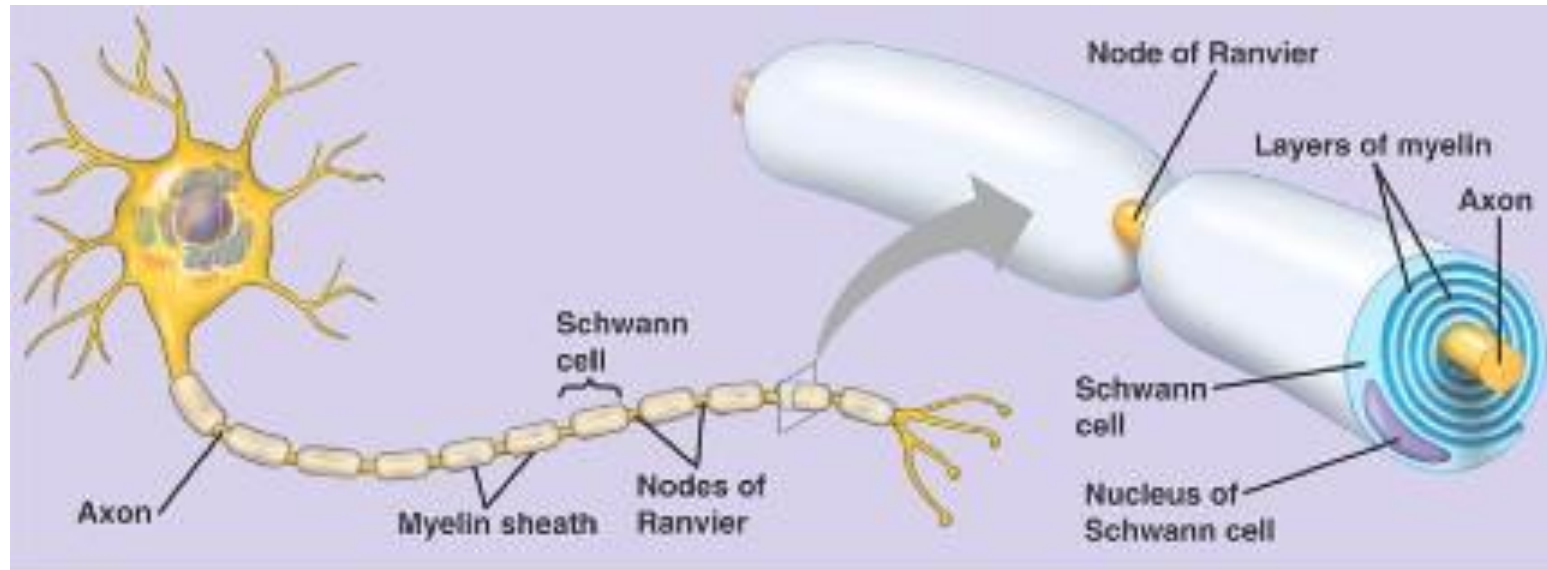


# Sphingomyelin & Myelination

- Myelination is a process of wrapping of highly specialized myelin membrane (sheath) around axons of a neuron by specialized brain cell (Oligodendrocytes)

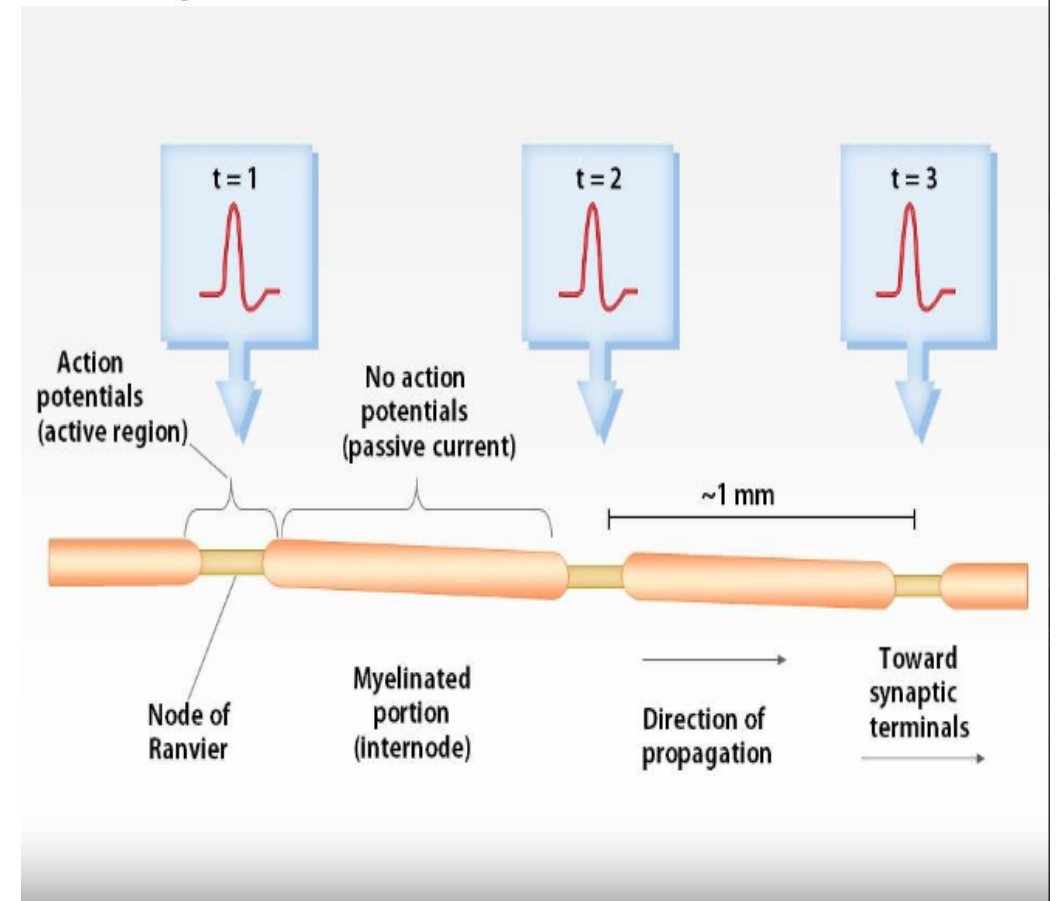


# Myelination



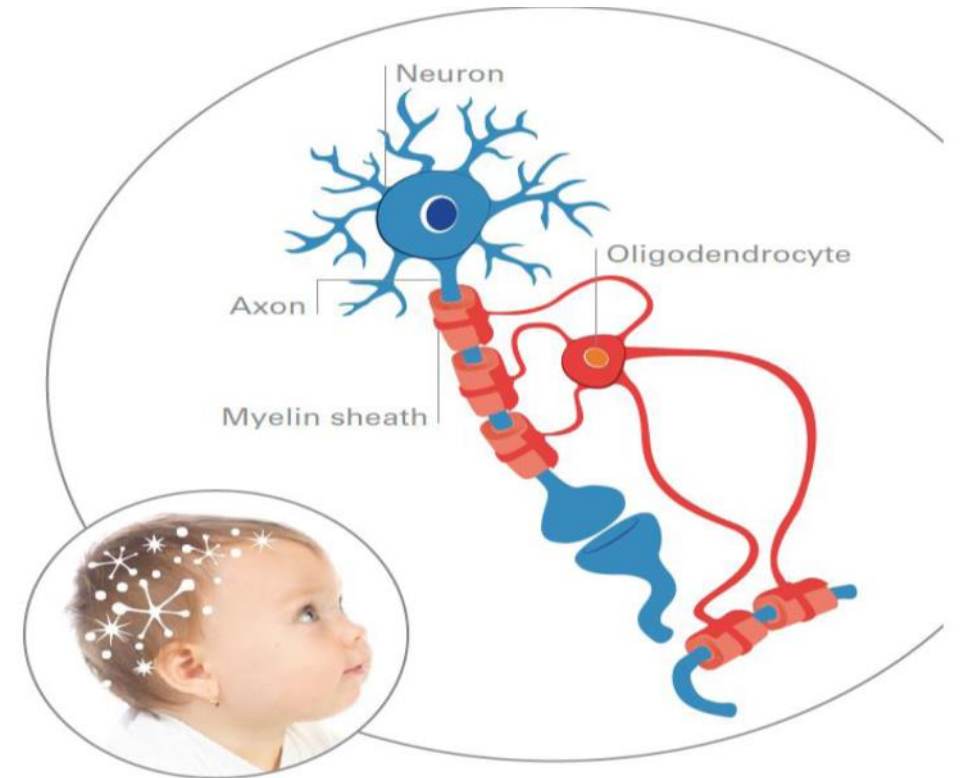
- Myelin sheath enables action potential to be propagated along the axon in a saltatory fashion with higher speed and less energy consumption;
  - By localizing voltage gated  $\text{Na}^+$  channels to short gap btw adjacent sheaths
  - By acting as electrical insulators

## Saltatory Conduction



# Myelination is a crucial part of neurodevelopment <sup>1,2</sup>

- Ensures fast, efficient & synchronized communication between cells and networks
- Protects the neuron
- Matures alongside cognitive and behavioural development





# Nutrition & Myelination

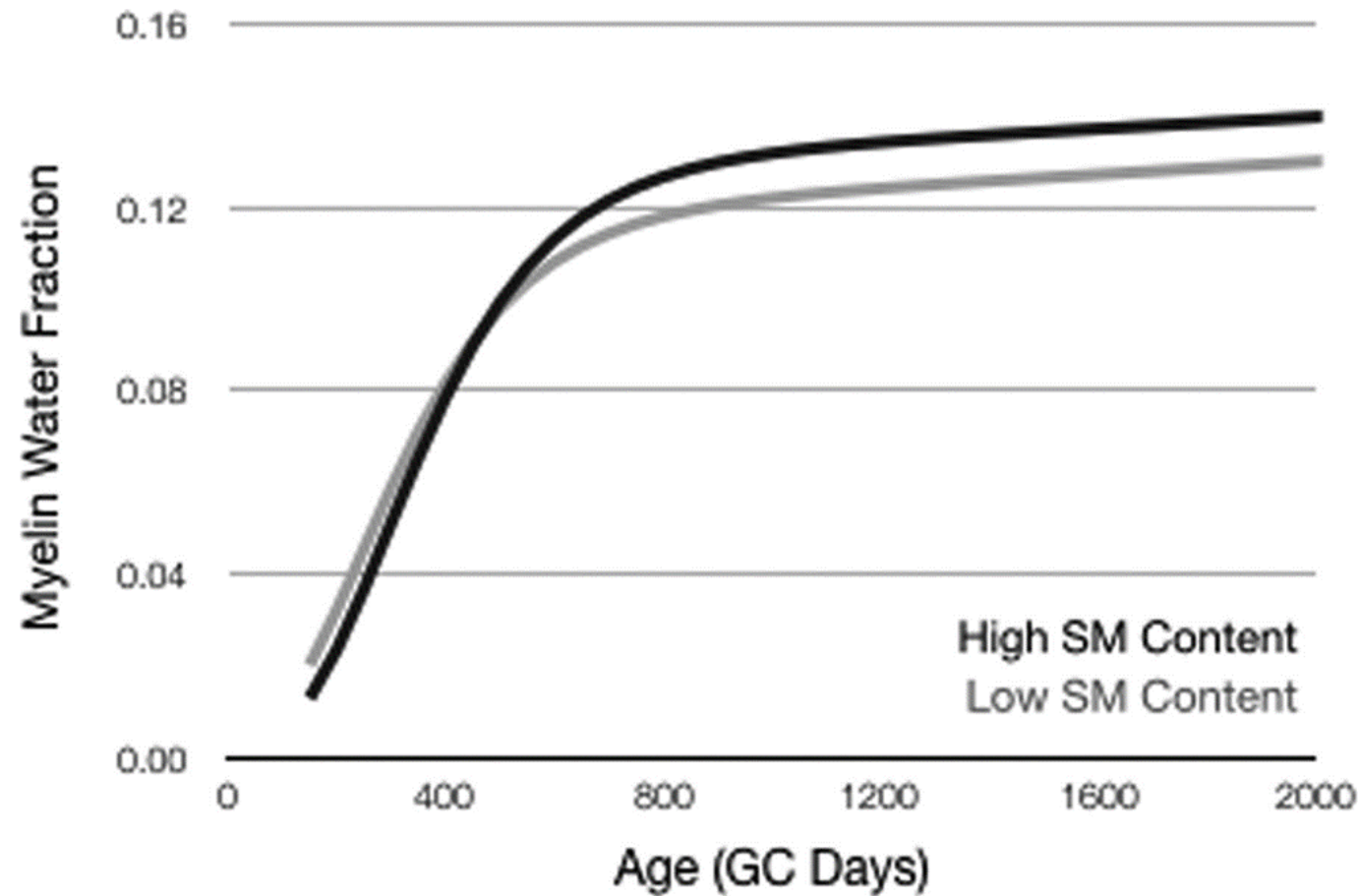
- Early life nutrition is an important modifiable factor that determine myelination & consequently cognitive functioning

## *Essential Nutrients for Brain Myelination*

- Long Chain Polyunsaturated fatty acids;
  - DHA – docosahexanoic acid
  - ARA – Arachidonic acid
- Phospholipids;
  - **Sphingomyelin**
  - Phosphotidylcholine
- Minerals – zinc, Iron,
- Choline, Cholesterol etc

- Deficiency of these nutrients is associated with;
  - Altered myelin content, composition & morphology
  - Potential for disruption of normal brain function
  - Impaired cognitive outcomes

# Positive correlation between dietary sphingomyelin & brain myelination



# ROLE OF SPHINGOMYELIN IN COGNITIVE FUNCTION

# What is cognition?

- The mental process of acquiring knowledge and understanding through thought, experience and the senses
- It is the emergence of the ability to think and understand
- These processes include thinking, knowing, remembering, judging and problem-solving





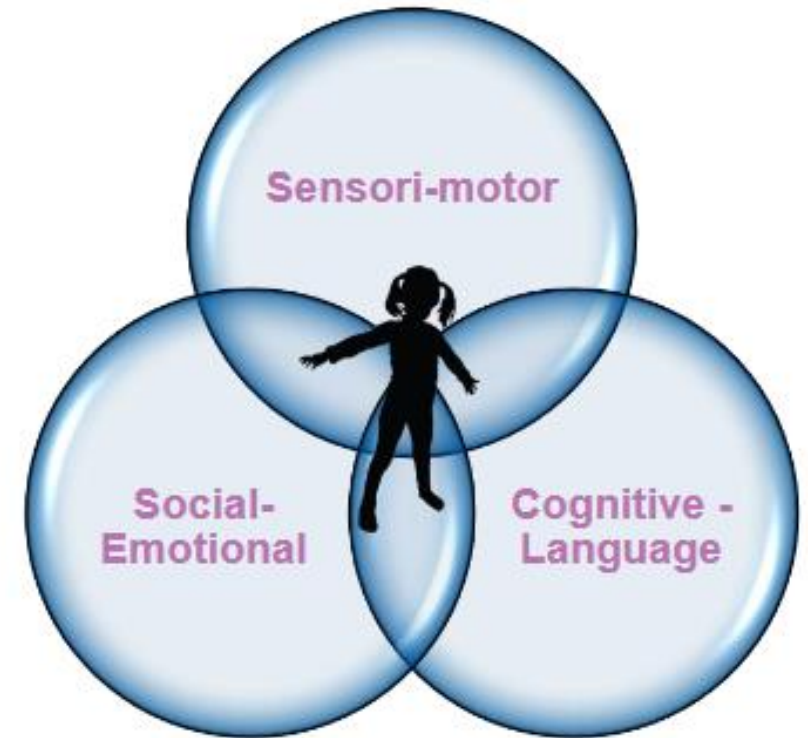
- Cognition involves

- Transforming sensory input
- Reducing sensory information
- Elaborating information
- Storing & recovering information
- Using information

# Cognitive Development

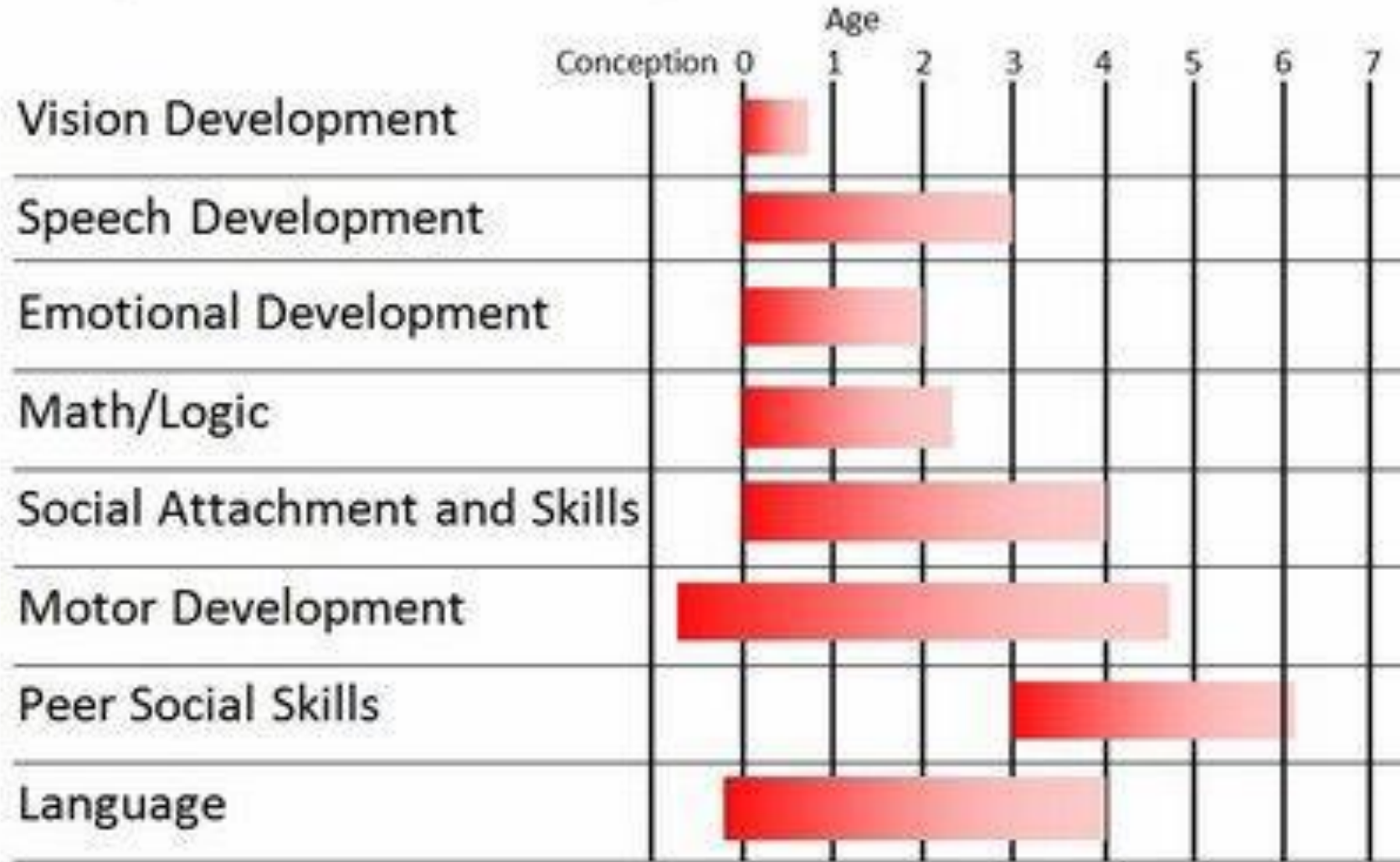
- Changes in neurobiology parallel behavioral maturation milestones<sup>1</sup>
- Continuous learning process of gaining:
  - Sensory
  - Motor
  - Cognitive
  - Language
  - Social &
  - Emotional abilities

• <sup>1</sup>Silbereis et al., 2016





## Stages of Brain Development in an Infant



# Myelination & Cognition

- Early myelination trajectories are associated with development of cognitive abilities & outcomes<sup>1</sup>
- There is a strong correlation btw emergence of specific cognitive function and myelination of brain regions and networks subserving that function<sup>2</sup>

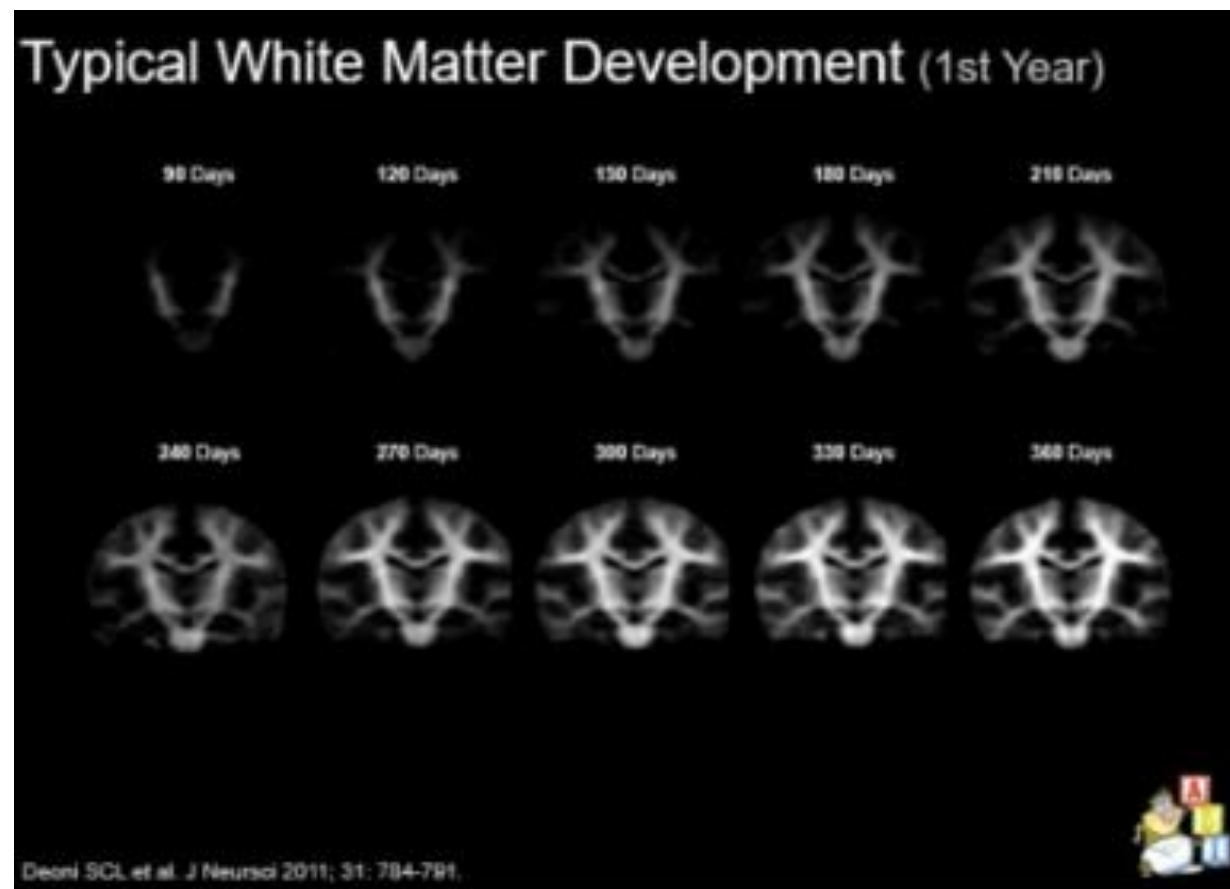
• <sup>1</sup>Muircheartaigh et al 2014; <sup>2</sup>Fornari et al 2007

- Brain myelination promotes:
  - General cognitive ability
  - Language and reading ability
  - Working memory
  - Processing speed
  - Sensory reactivity

# Myelination & Cognition

Clinical studies demonstrate the link between myelination and cognition, including:

- general cognitive ability<sup>1</sup>
- language<sup>2</sup> & reading<sup>3</sup>
- working memory<sup>4</sup>
- processing speed<sup>5</sup>
- sensory reactivity<sup>6</sup>



*Schmithorst et al., 2005; Deoni et al., 2015; <sup>2</sup>Büchel et al., 2004; O'Muircheartaigh et al., 2013; <sup>3</sup>Nagy et al., 2004; Beaulieu et al., 2005; <sup>4</sup>Nagy et al., 2004; Short et al., 2013; <sup>5</sup>Turkmen et al., 2008; Bartzokis et al., 2010; Lu et al., 2013; <sup>6</sup>Weinstein et al., 2014*

# Myelination & Cognition

## Objective

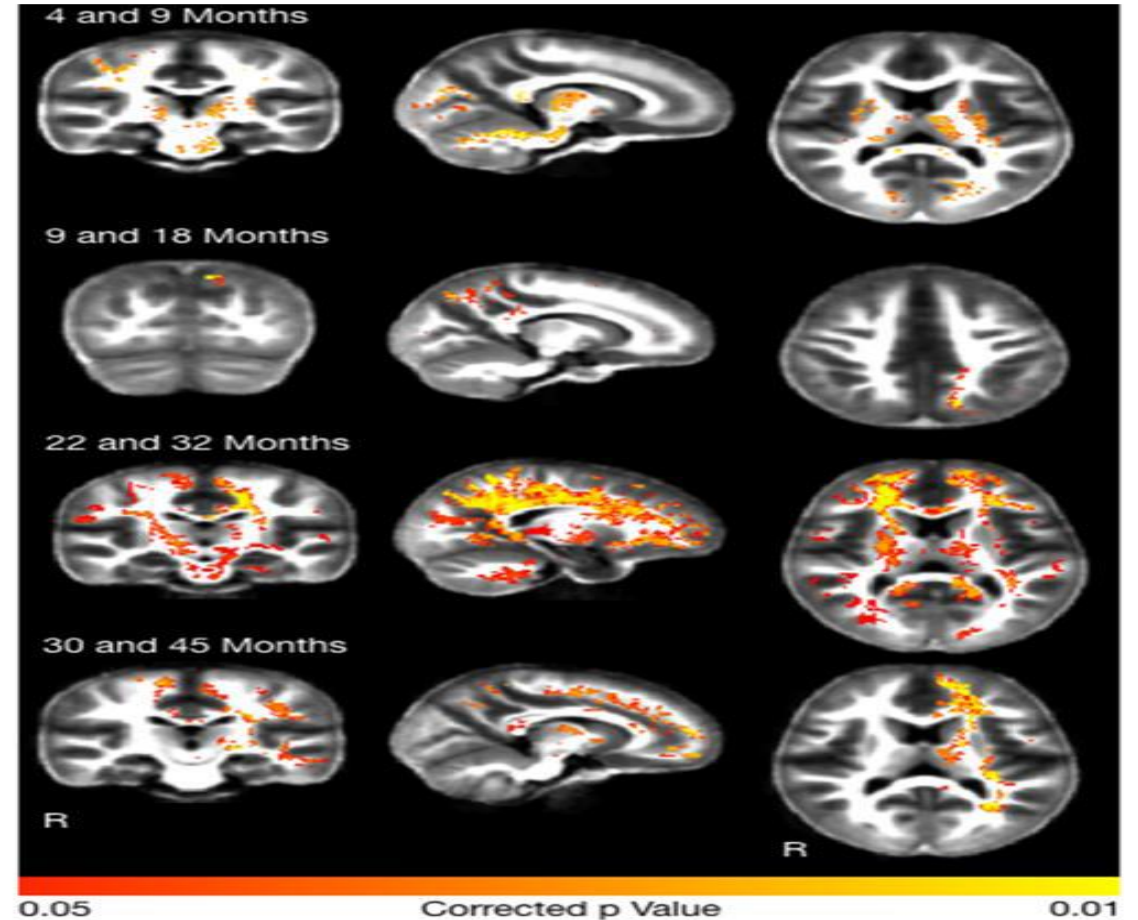
To examine the longitudinal relationship of maturing brain myelination to variability in cognitive skills.

## Population

N = 187 children with repeated MRI (Myelin Water Fraction) and cognitive assessments (MSEL) between 2 months and 6 years of age

## Results

Marked age-related variability in repeated cognitive measures that was variably related to on-going changes in myelination



# Brain Synaptic plasticity – the key to brain efficiency

- The different parts of the brain have different functions.
- Efficient connectivity is mandatory for proper brain and cognitive functions
- It is the connections between the neurons that make the brain work



# Breast vs Formular feeding & Cognition

- Deoni & colleagues observed differences btw breast and formula fed infants in improved performance on test of cognitive function
- even after controlling for birthweight, pregnancy length, parent education level and socioeconomic status,

Deoni et al 2019

# *Differences in Lipids & Micronutrient composition of Formula*

- Subanalysis of lipids & micronutrients of contents of different formula reveal;
  - Significant and consistent differences in the profiles of myelination & cognitive maturation
  - With children who had the lowest myelin development overall having the worst cognitive scores and vice-versa
  - Formula with the highest myelin levels & cognitive scores also had the highest concentration of LC-PUFA (DHA, ARA), Choline, Folic acid, Sphingomyelin & Phosphatidylcholine.



## *Take home messages*

- The first 3 years of life represent a rapid and dynamic period of brain maturation
- Most brain processes during the period are primarily focused on connecting the brain by myelination and formation of new brain connections
- Early life nutrition is an important and modifiable factor that can shape synaptogenesis, myelination and subsequently cognitive outcomes

## *Take home messages*

- SM plays an important role in cognitive development via its structural and functional involvement in CNS myelination & synaptic plasticity.
- CNS myelination as well as synaptic plasticity are important in the maturation of brain networks, coordinated information processing and ultimately cognitive performance in infants and children
- Human milk is the preferred source of nutrition for infants and naturally contains Essential nutrients for development of synapses, myelination and cognitive functions!

## References

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Thank you!

