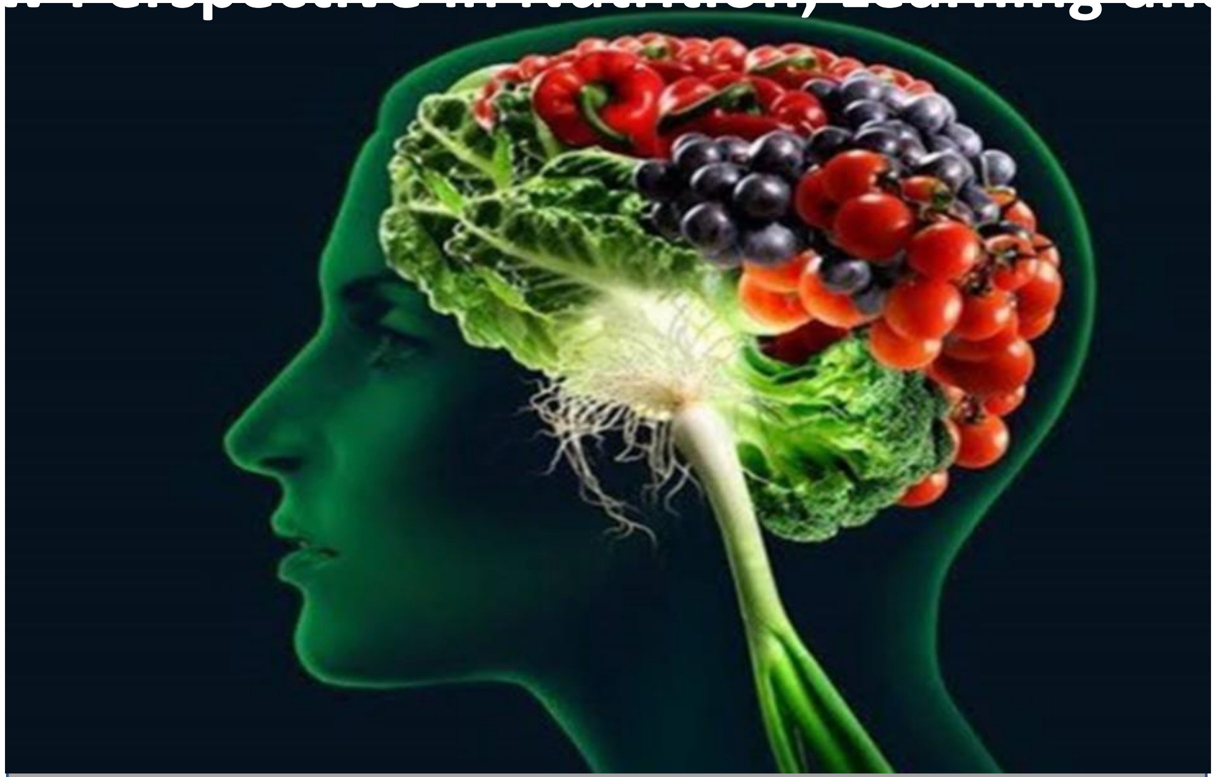
Human Milk Oligosaccharides(HMOs) and Brain Development: Key Perspectives

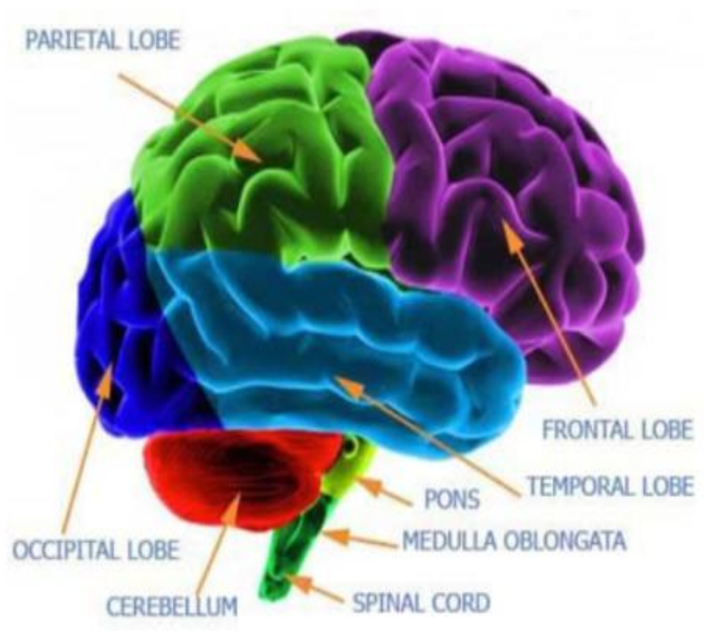


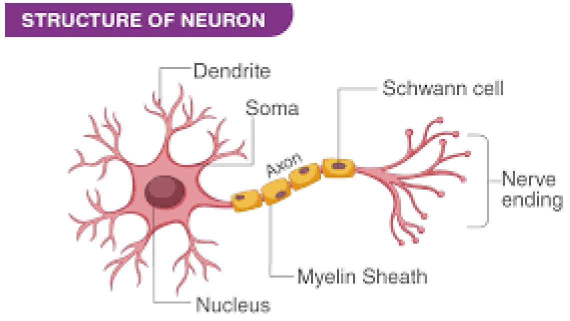
This presentation is for Healthcare Professionals ONLY

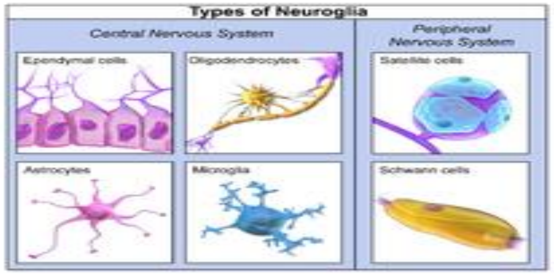
Outline of Presentation

- Overview of the brain structure and functions
- Brain development in early childhood
- Infant nutrition in learning
- Human Milk Oligosaccharides (HMOs)
- HMOs in brain development: New perspectives
- Conclusions

Brain Structure

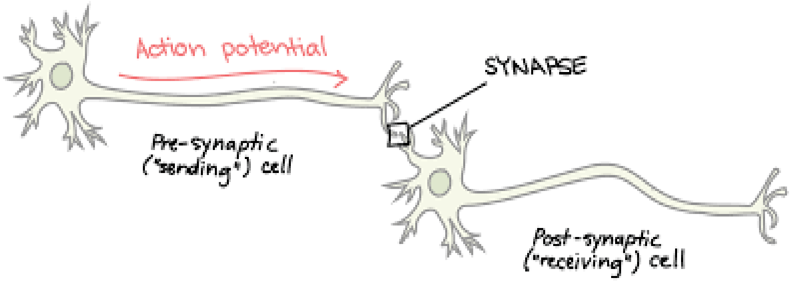






- Neurons (nerve cells)
- 100 billion neurons (100,000,000,000)
- 100 km of nerves

- 100 billion non-neuron cells (100,000,000,000)



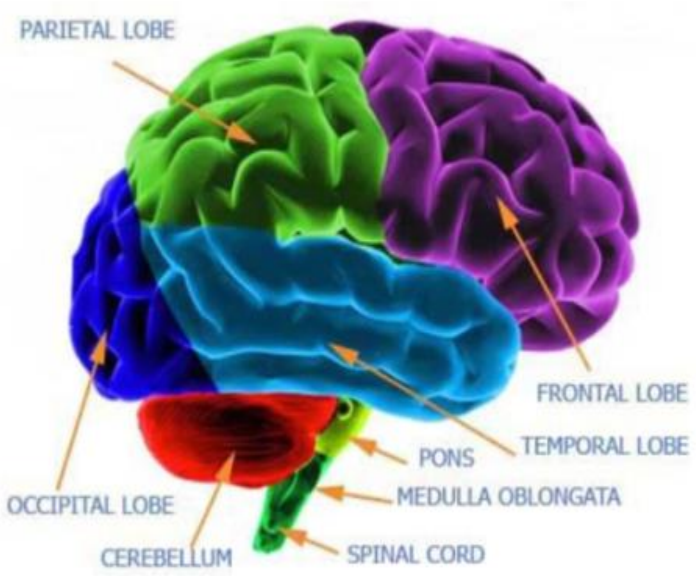
1 quadrillion synapses (1,000,000,000,000,000)

- 600 km of blood vessels[3]

Kasthuri N, et al. 2015[2]

.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.

FUNCTIONS OF THE BRAIN



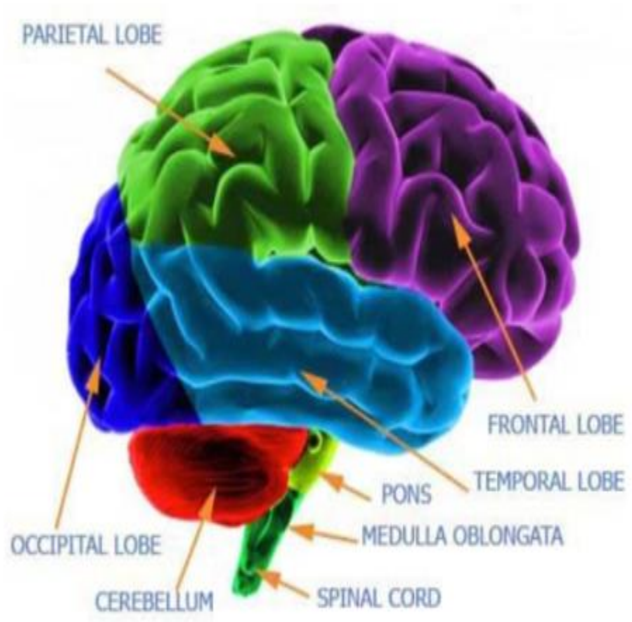
FRONTAL LOBE

- Attention and concentration
- Organization
- Expressive language
- Motor planning and initiation
- Personality
- Problem solving
- Emotion

BRAIN STEM

- Breathing
- Arousal and consciousness
- Heart rate
- Sleep and wake cycle

FUNCTIONS OF THE BRAIN



TEMPORAL LOBE

- Learning and Memory
- Understanding language (receptive language)
- Sequencing
- Hearing
- Organization

OCCIPITAL LOBE

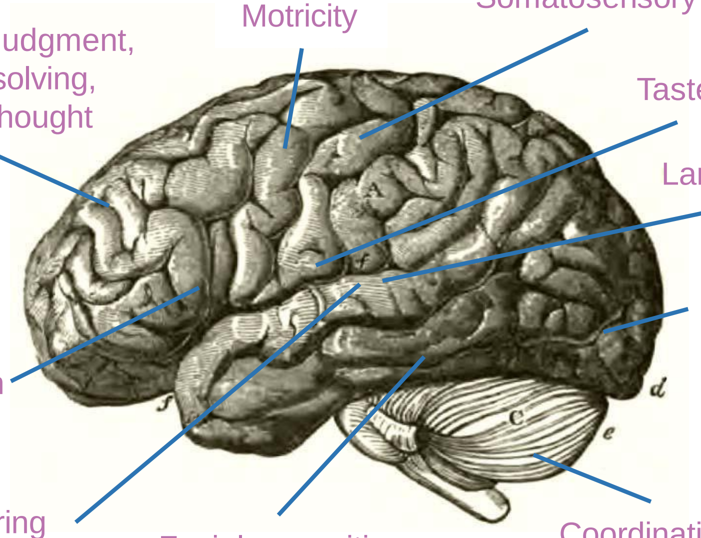
- Vision

PARIETAL LOBE

- Sense of touch
- Spatial perception
- Differentiation
- Visual perception

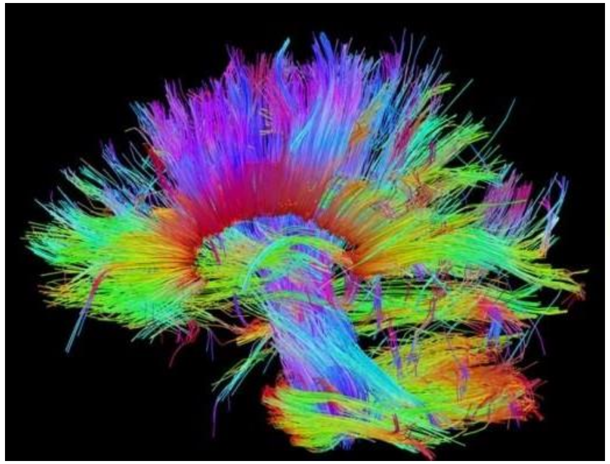
- **TEMPORAL LOBE**
- Balance
- Skilled motor activity
- Co-ordination

Functions of the various parts of the brain

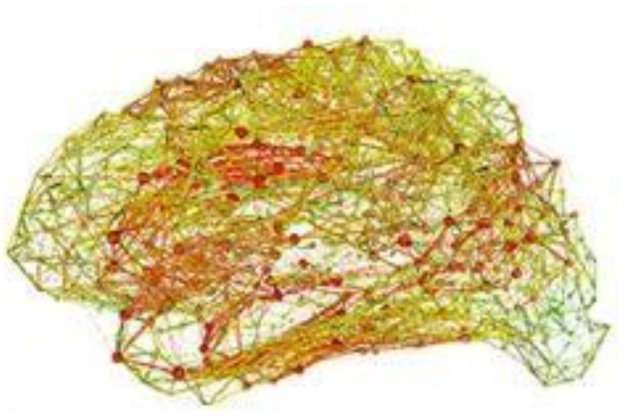


Ackerman S, 1992[1]

Brain functional connectivity



Source: Human Connectome Project[2]



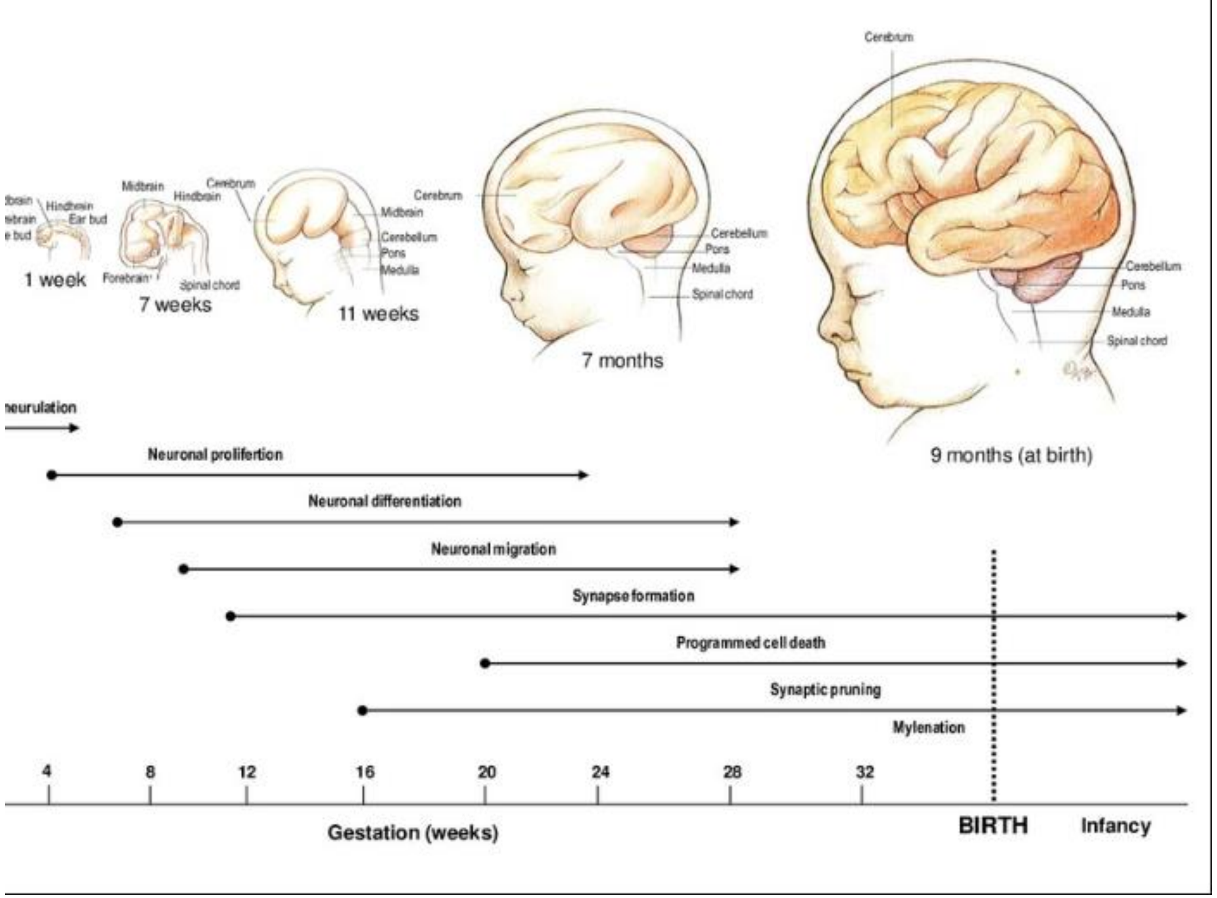
van den Heuvel & Sooms, 2011[3]

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

The Development of the Child Nervous System

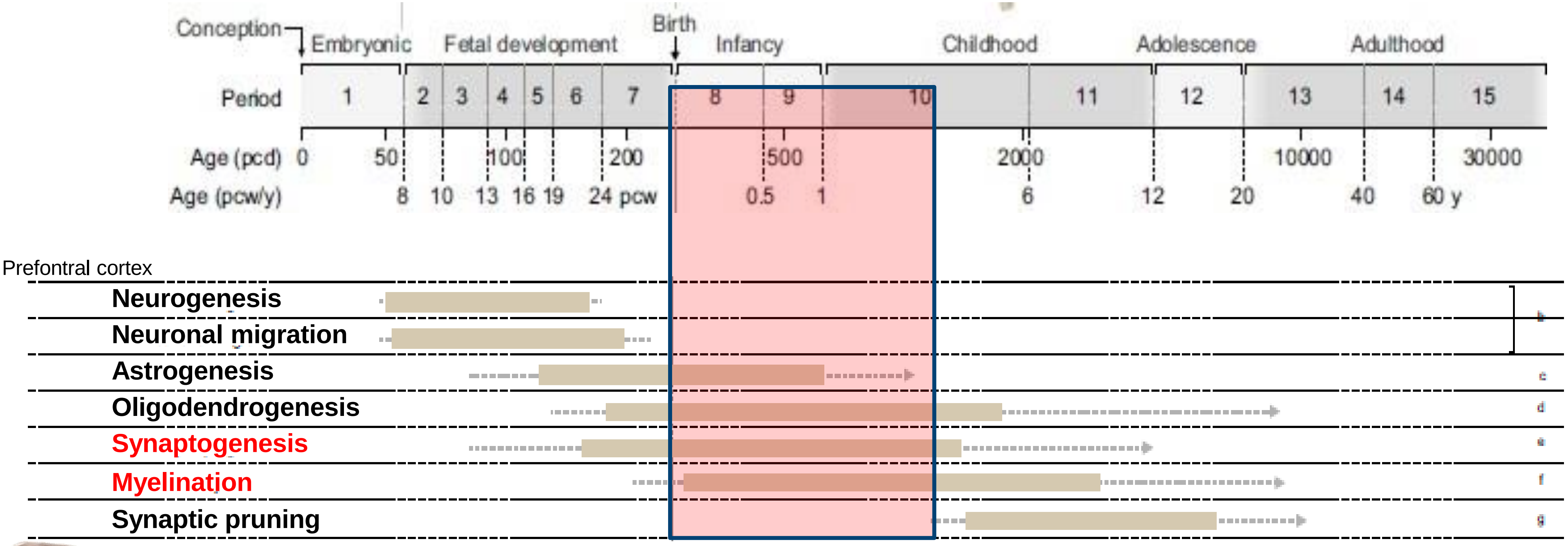
- The foetal nervous system is one of first systems to develop and the last to be completed after birth
- The process generates the most complex structures within the embryo
- The brain weighs 300-350 grams at birth and contains 100 billion neurons



Development of The Child Nervous System

- At birth, the average baby's brain is about a quarter of adult brain.
- Doubles in the first year.
  - Critical period
  - Undergoes rapid growth in the first 6 months of postnatal life
- 80% of adult size by age 3.
- 90% – nearly full grown – by age 5 to 6.

Timeline of key human neurodevelopmental processes



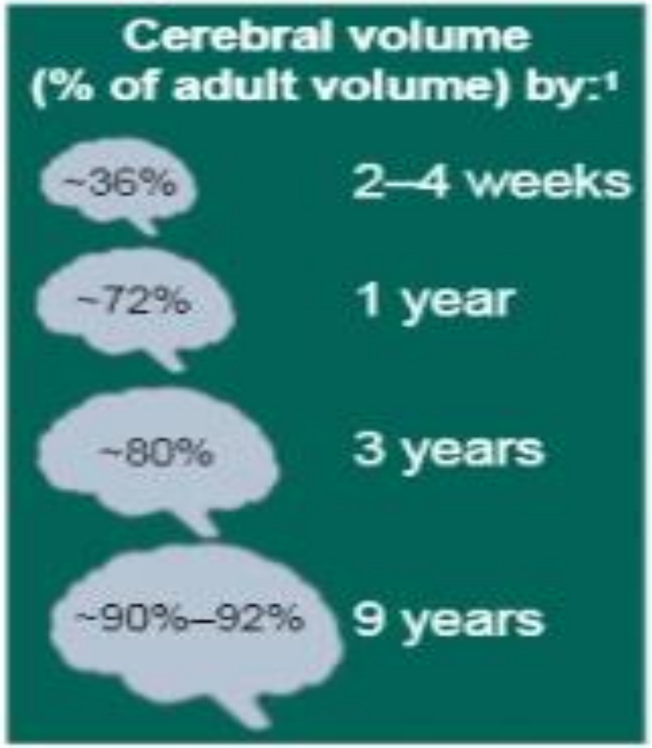
Adapted from Silbereis JC, et al., Neuron 2016;89:248–68

- 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]

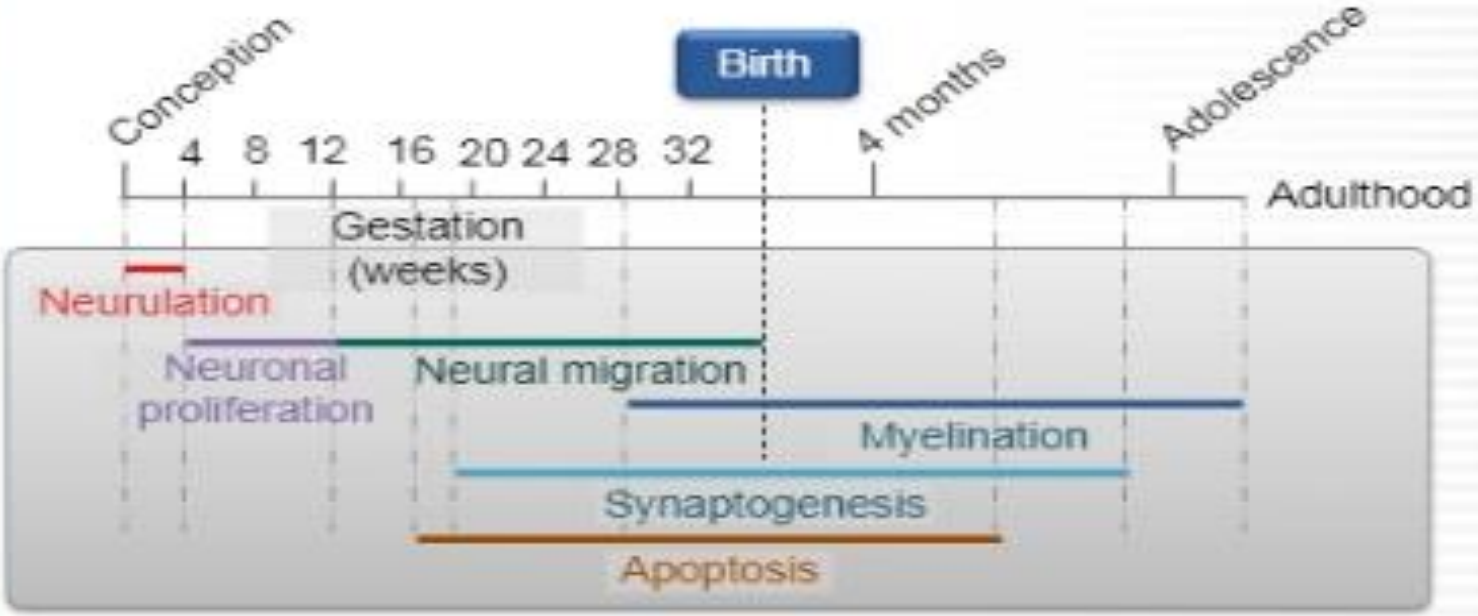
pcd, post-conceptional days, pcw,/y post=conceptional weeks/years; y years.

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

Brain Development in Children



Timeline of major events in brain development[2]



The brain volume achieved at the end of the first year is an important indicator of later intelligence.[1]

1. Choe MS, Ortiz-Mantilla S, Makris N, *et al. Cereb Cortex.* 2013;23(9):2100–2117.
2. Tau GZ, Peterson B. *Neuropsychopharmacology Rev.* 2010;35:147–168.

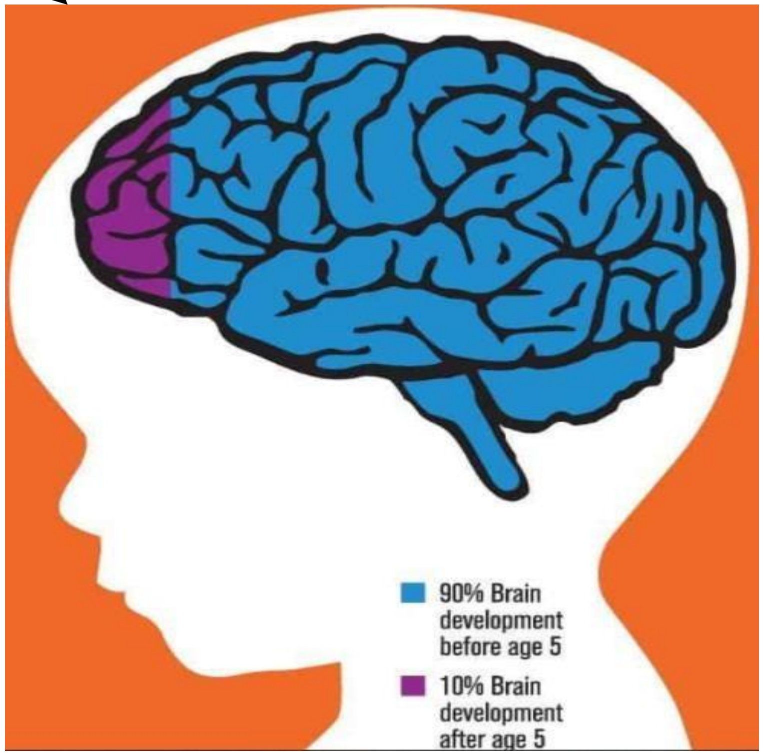
Brain Development

NATURE

Genetic expression

NURTURE

Environmental factors



Key Factors Influencing Brain Development

NATURE AND NURTURE

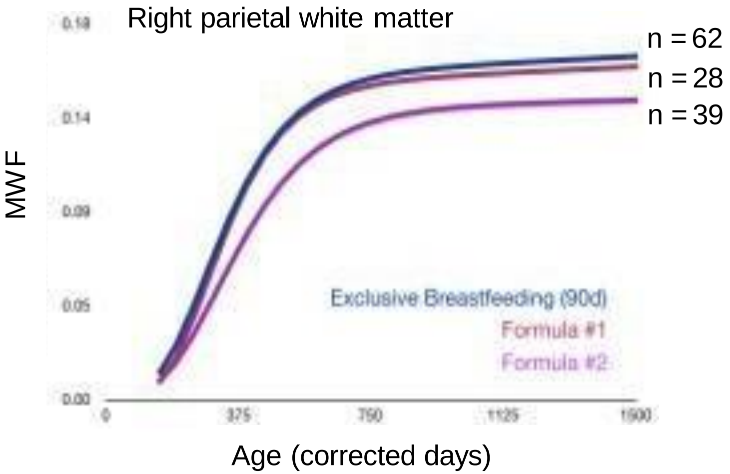
- **Nature (Gene Expression)**

- **Nurture (Environmental factors):** The developing brain is vulnerable to modification by environmental factors

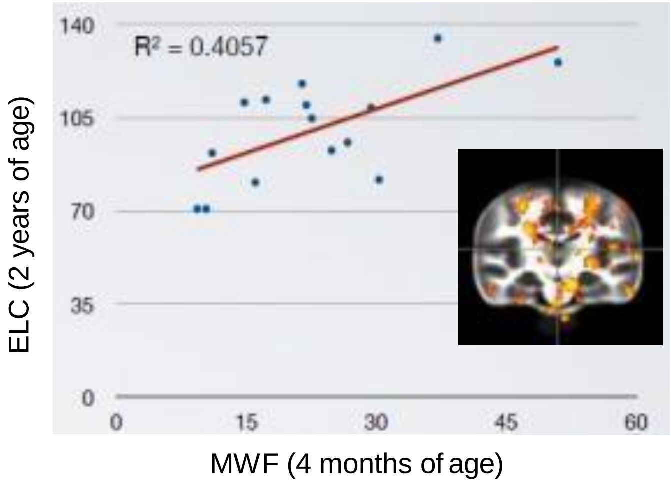
  - Socioeconomic status
  - Stress
  - Pollution
  - Urbanization
  - Social Interactions
  - **Nutrition**

Interplay between structural functional development and nutrition

Nutritional sensitivity

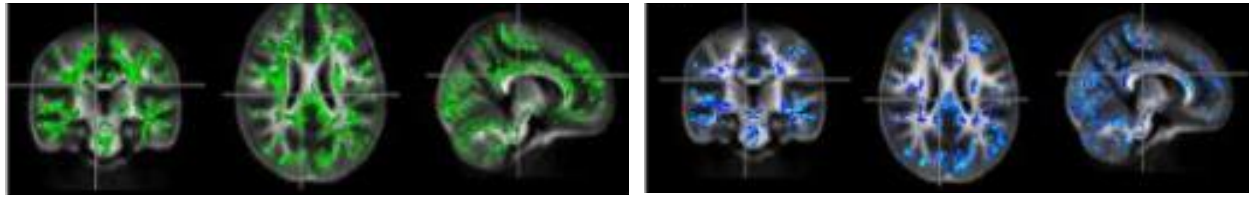


Predictability



Correlation between MWF and the cognitive development. N. Schneider & S. Deoni, personal communication

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

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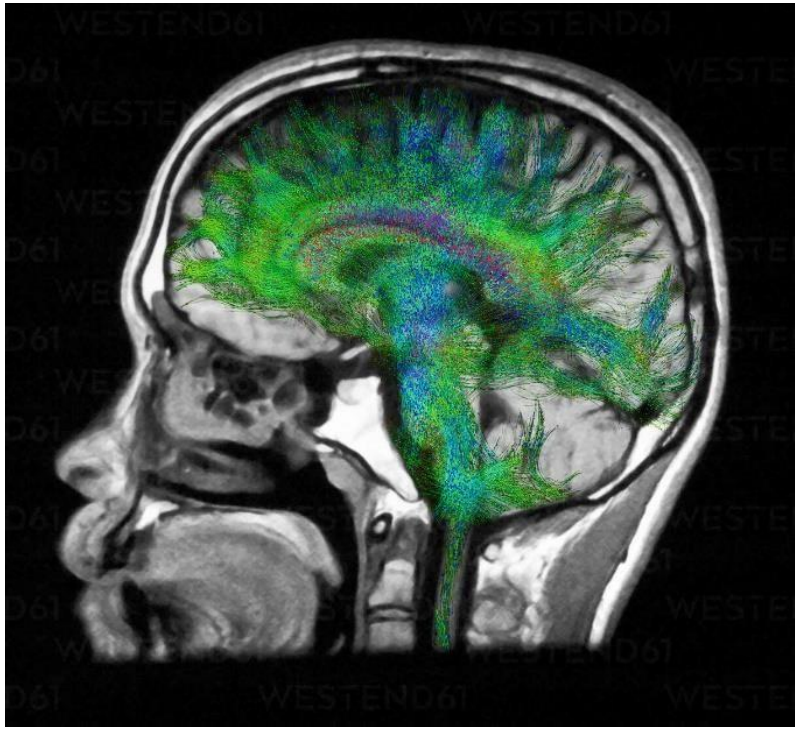
ARA, arachidonic acid; DHA, docosahexaenoic acid; MWF, myelin water fraction.
Deoni S, et al. *Neuroimage* 2018;178: 649-59

Key Nutrients Supporting Brain Growth and Development

Choline

Sphingomyelin

Iodine



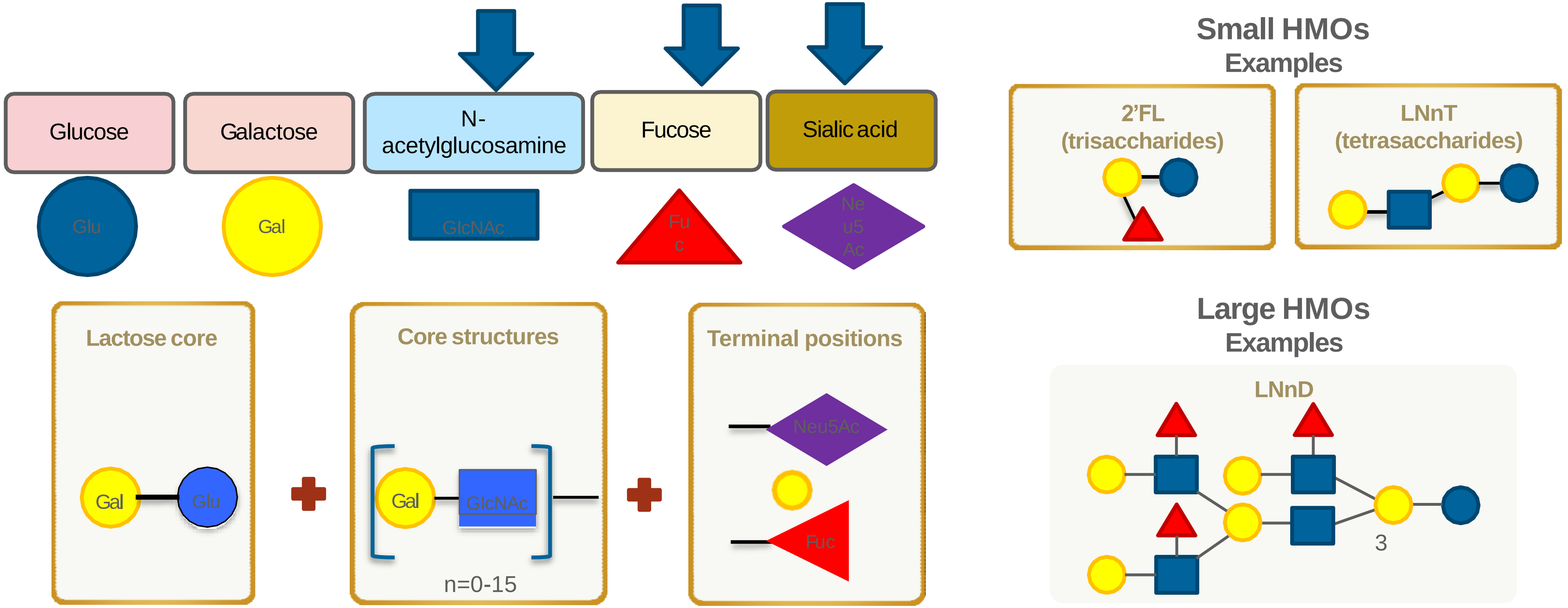
Lutein

DHA

HMOs

Structure of HMOs: Fucosylated and Sialylated

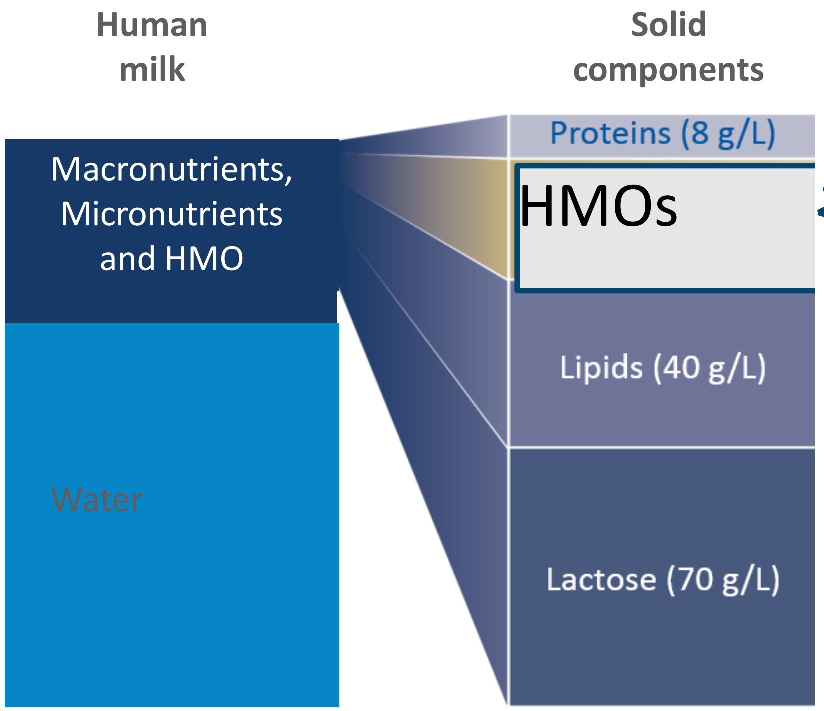
Building blocks and main structures



Small HMOs such as 2'FL and LNnT form the largest group of HMOs in human milk.[1-3]

2'FL, 2'fucosyllactose; LNnD, lacto-N-neo-difuco-hexaose; LNnT, lacto-N-neotetraose.

HUMAN MILK OLIGOSACCHARIDES (HMOs)



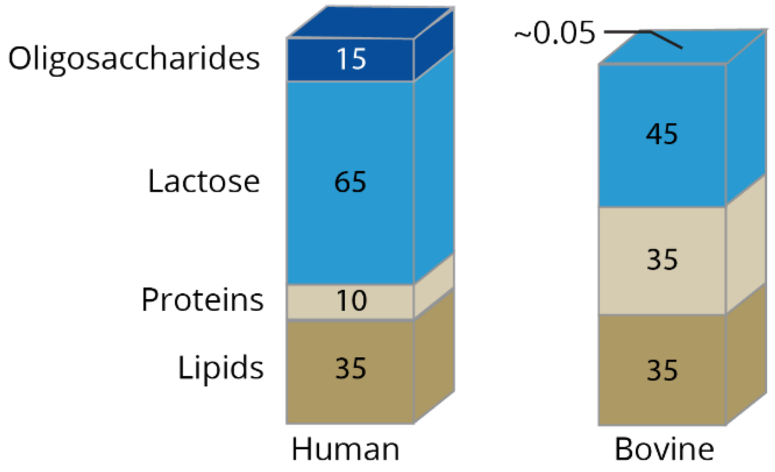
HMOs are the third largest solid component in breast milk

HMO levels range between: 20 - 25 g/L for colostrum and 5 and 15 g/L for mature milk[1,2]

The HMO fraction is larger than that of proteins and can therefore be considered a key component of human breast milk.[1,2]

Difference between Human and Bovine milk

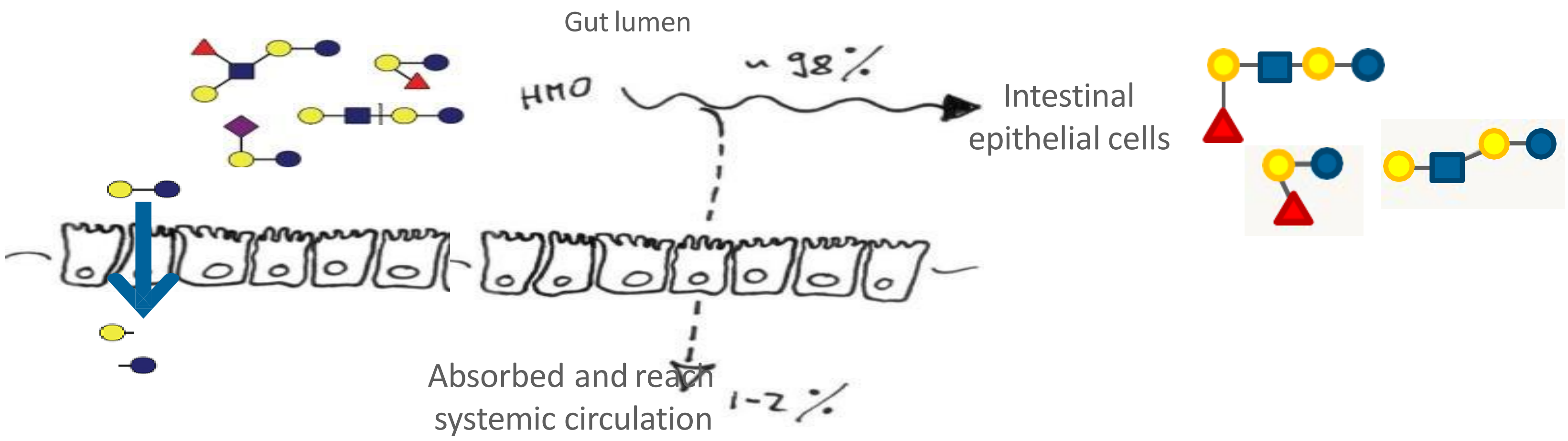
	Human Milk	Bovine Milk
Oligosaccharides (g/L)	10-15	~0.05
Number of identified oligosaccharides	>200	~40



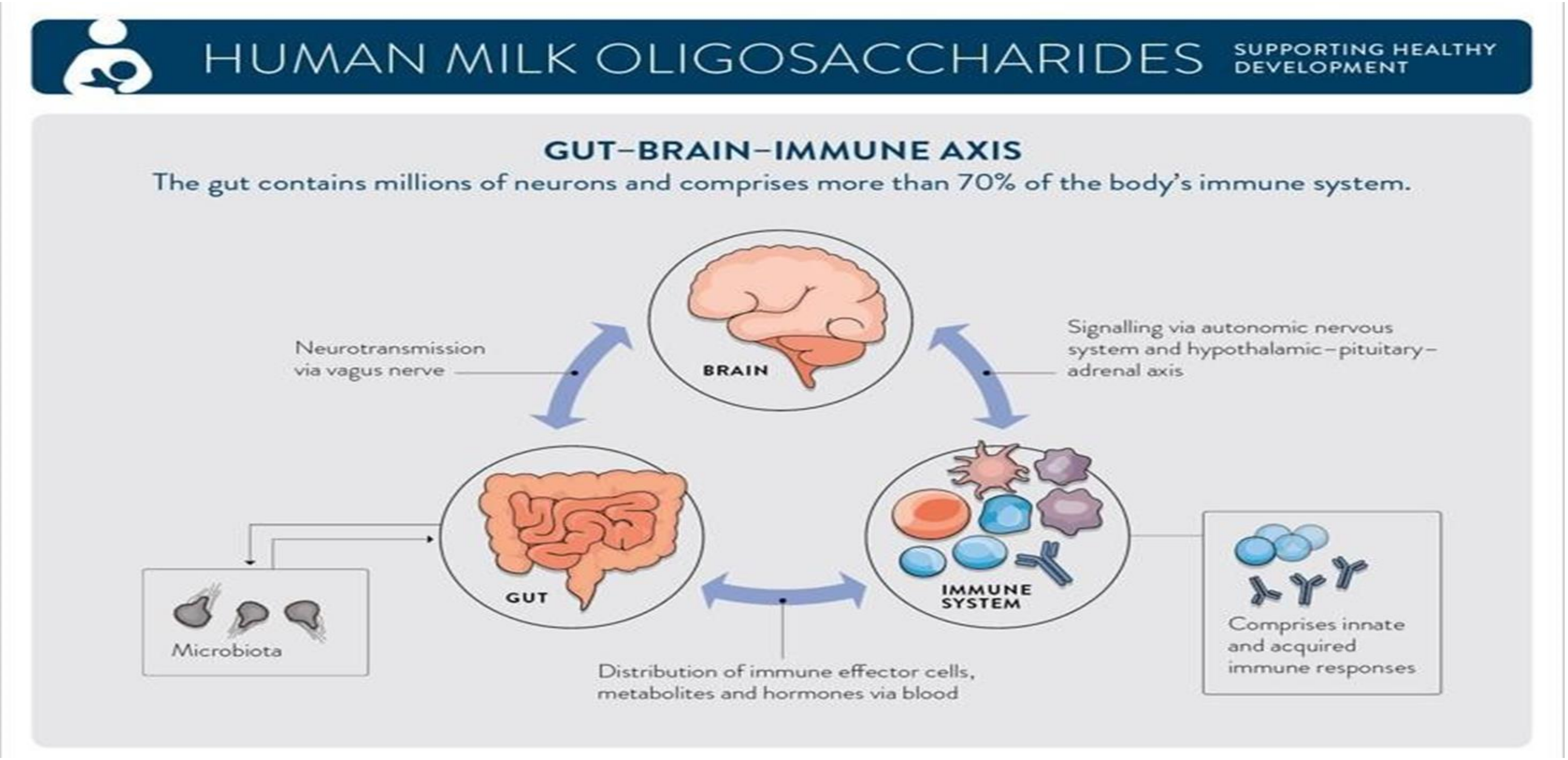
% neutral fucosylated	50%-80%	~1%
% sialylated acidic	10%-20%	~70%

Metabolism of HMOs

- Infant gut cannot digest HMOs because of lack of the necessary enzymes
- Reaches the lower gut unchanged
- Only ≈ 1-2% of HMOs are absorbed in the gut and enter the systemic circulation
- The rest remain in the gut,
  - Modulates gut microbiota
  - Metabolize into SCFA, GABA etc and participate in the **Gut-Brain Cross Talk**



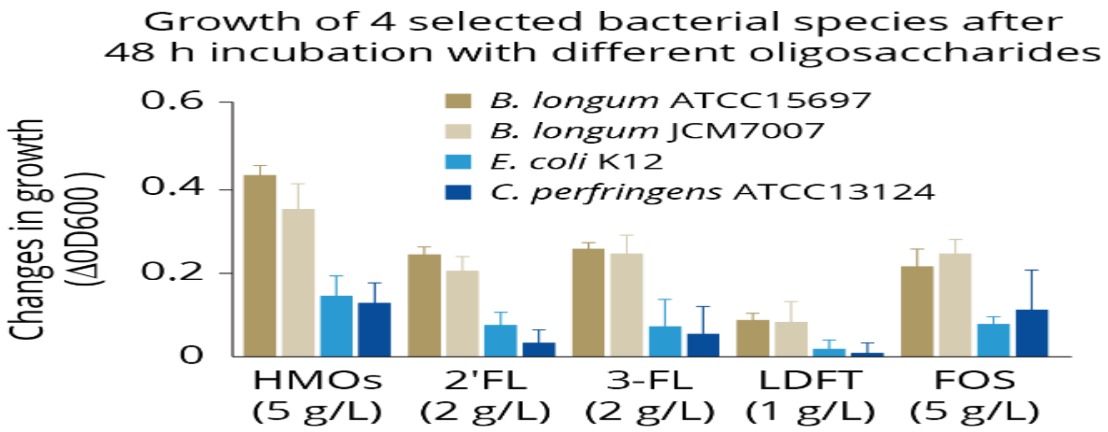
Adapted from Rudloff S et al., 2012.



SCFA cross the BBB to modulate structural and functional aspects of the Brain, affect the immune response via regulation of dendritic and T-cell function, as well as via inhibition of cytokine production

2´FL promotes the growth of specific bifidobacteria

- HMOs such as 2´FL and 3´FL were able to promote the growth of bifidobacterial strains and to suppress potentially pathogenic bacteria
- When supplemented with 2´FL, the bifidobacterial strains multiplied abundantly and produced ample SCFA

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GLYCOBIOLOGY

Article Navigation

The principal fucosylated oligosaccharides of human milk exhibit prebiotic properties on cultured infant microbiota FREE

Zhuo-Teng Yu, Ceng Chen, David E Kling, John M McCoy, Massimo Merighi, Matthew Heidtman, David S Newburg

Author Notes

Glycobiology, Volume 23, Issue 2, February 2013, Pages 169–177, https://doi.org/10.1093/glycob/cws138

B. longum ATCC15697, *B. infantis;* FL, fucosylated; FOS, fructo-oligosaccharide; HMO, human milk oligosaccharide; LDFT, Lactodifucotetraose; SCFA, short-chain fatty acid.

The Journal of Nutritional Biochemistry
Volume 31, May 2016, Pages 20-27

Oral supplementation of 2′-fucosyllactose during lactation improves memory and learning in rats ☆

Elena Oliveros [a], María Ramirez [a], Enrique Vazquez [a], Alejandro Barranco [a], Agnes Gruart [c], Jose Maria Delgado-Garcia [c], Rachael Buck [b], Ricardo Rueda [a], Maria J. Martin [a]

Learning

Memory

Rat pups received an oral supplementation of 2'-FL or water (control group) during the lactation period. Thereafter, maintained on a rodent standard diet. Evaluated at age 4-6weeks and 1year, using classical behavioral tests. Both groups showed similar behavior when assessed just after weaning (age 4-6weeks), At age 1year, 2'-FL rats performed significantly better in the Novel Object Recognition compared to controls.

RESEARCH ARTICLE

Human milk oligosaccharide 2′-fucosyllactose links feedings at 1 month to cognitive development at 24 months in infants of normal and overweight mothers

Paige K. Berger[1], Jasmine F. Plows[1], Roshonda B. Jones[1], Tanya L. Alderete[2], Chloe Yonemitsu[3], Marie Poulsen[4], Ji Hoon Ryoo[1], Bradley S. Peterson[1], Lars Bode[3], Michael I. Goran[1] *

PLOS ONE | https://doi.org/10.1371/journal.pone.0228323 February 12, 2020

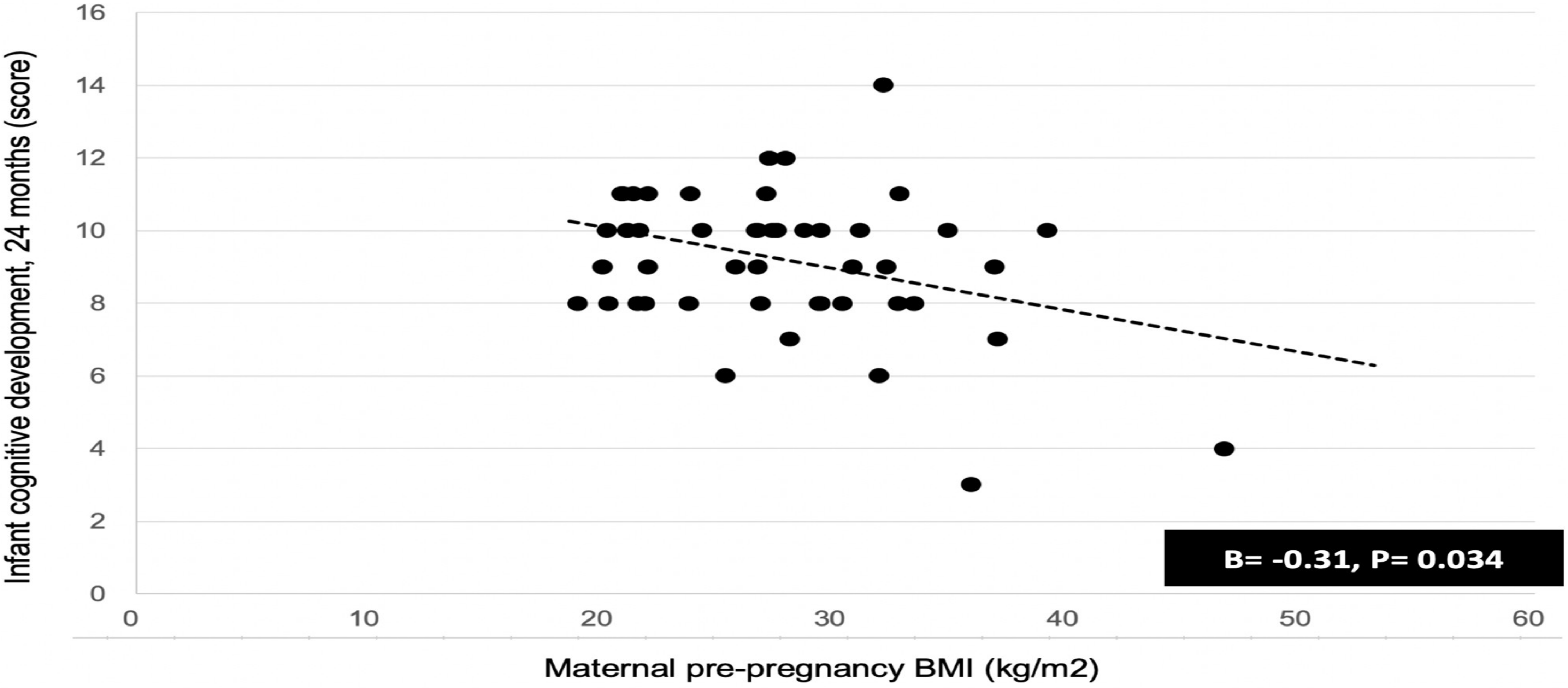
Objective

- To determine the impact of 2'FL from breast milk feeding on infant cognitive development at 24 months of age relative to maternal obesity and breast milk feeding frequency.

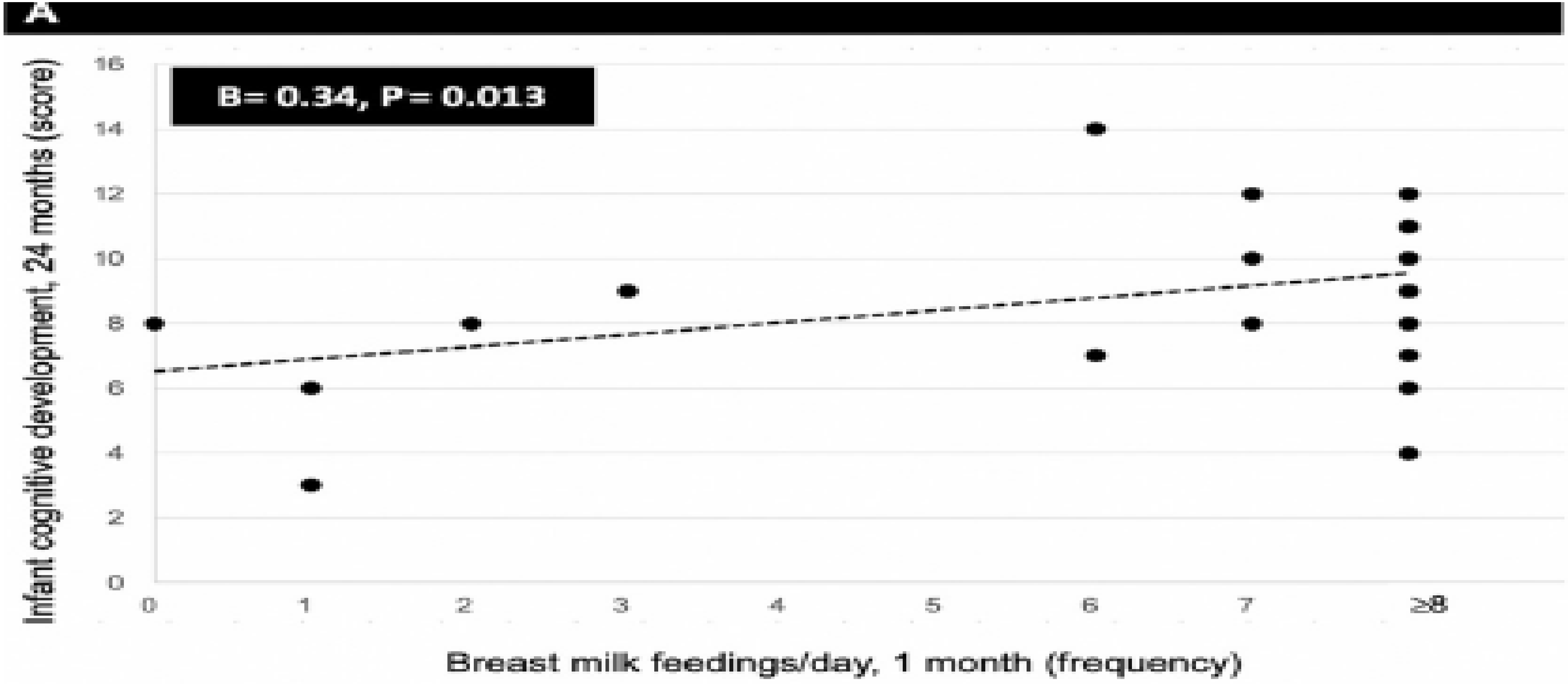
Materials and Methods

- Hispanic mother-infant pairs (n = 50) were recruited across the spectrum of pre-pregnancy BMI.
- Breast milk was collected at 1 and 6 months, and feedings/day were reported.
- Nineteen HMOs were analyzed using high-performance liquid chromatography, with initial interest in 2'FL.
- Infant cognitive development score was assessed with the Bayley-III Scale at 24 months.

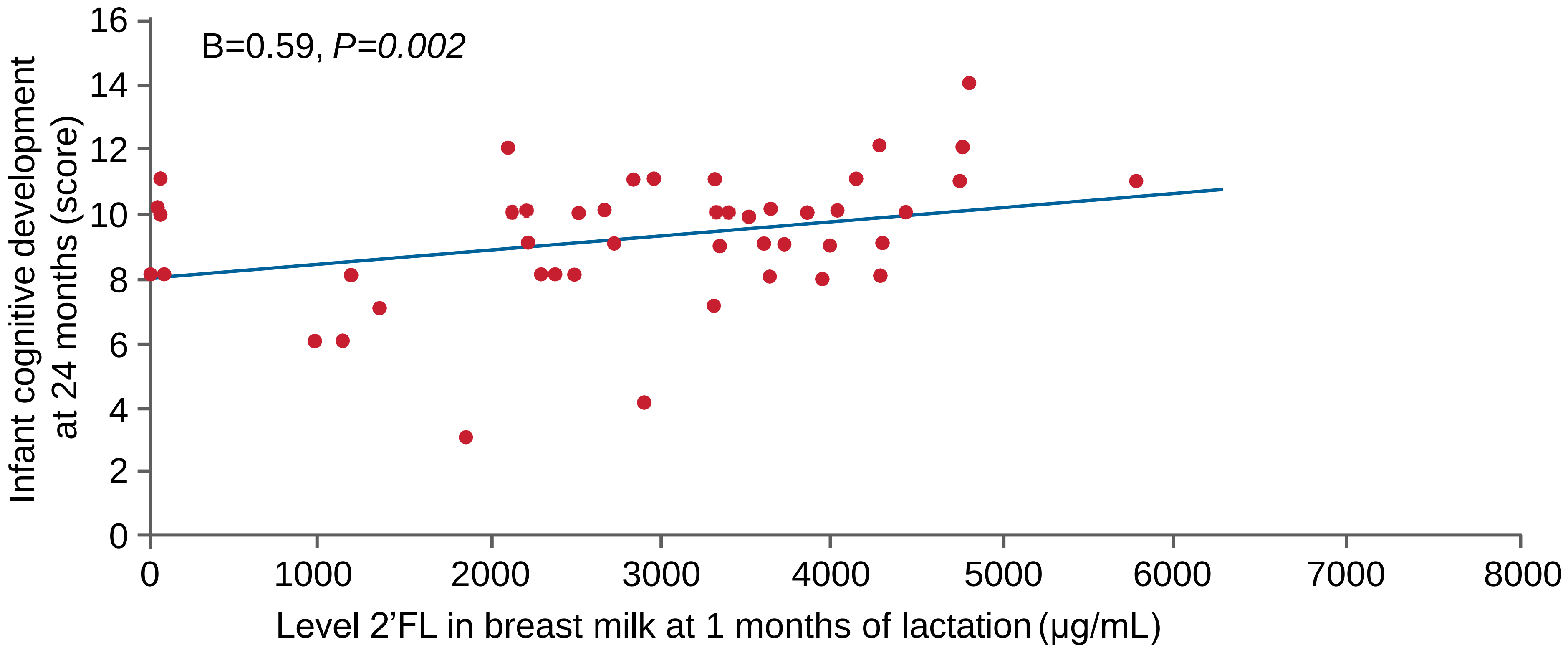
Maternal pre-pregnancy BMI related to infant cognitive development score at 24 months of age



Breast feeding frequency at 1 month is associated with better infant cognitive development at 24 months of age



2'FL in breast milk at 1 month is associated with better infant cognitive development at 24 months of age



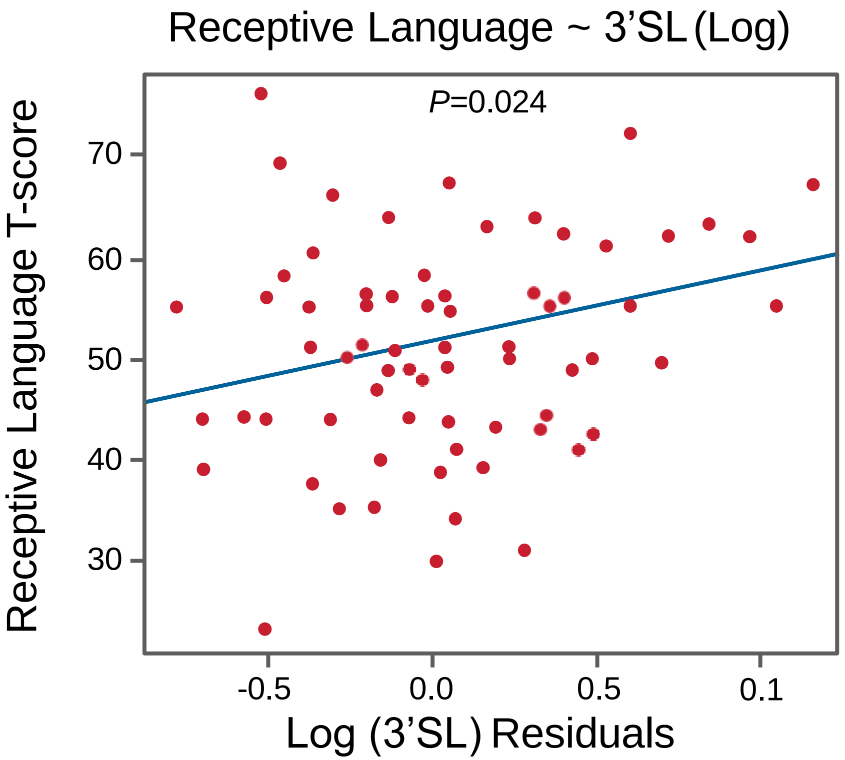
Adapted from Berger, et al. 2020.

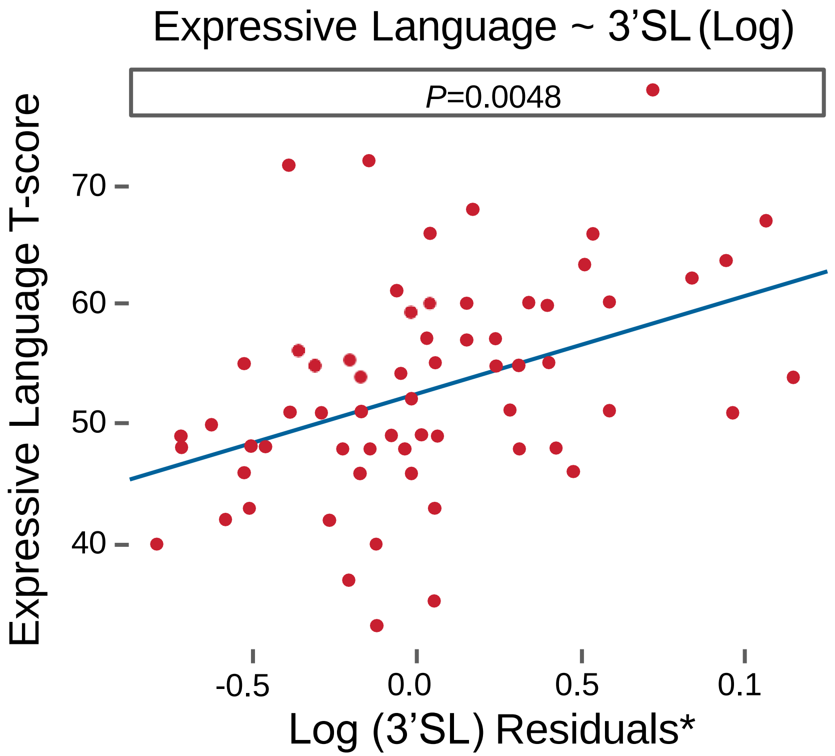
SL, sialyllactose.

A Positive Correlation between Breast Milk 3'-Sialyllactose and Language Development during Early Infancy. Seoyoon Cho et al.

- 99 healthy children were included in this analysis.
- The Mullen Scales of Early Learning was administered to assess the child's cognitive development.
- The concurrent breast milk samples (n=191) were obtained and analyzed for specific HMOs including 2'FL, 3'FL, 3'SL, 6'SL, Lacto-N-tetraose (LNT), Lacto- N-neotetraose (LNNT), Lacto-N-fucopentaose I (LNFPI), and A-tetrasaccharide (A-Tetra).

3’SL in breast milk is positively associated with language development in early childhood





*age-corrected 3’SL levels, expressed as difference to the population mean

Adapted from Cho, et al. 2020.

SL, sialyllactose.

Associations of human milk oligosaccharides and bioactive proteins with infant growth and development among Malawian mother-infant dyads

Josh M Jorgensen,[1] Rebecca Young,[1] Per Ashorn,[2,3] Ulla Ashorn,[2] David Chaima,[4] Jasmine CC Davis,[5] Elisha Goonatilleke,[5] Chiza Kumwenda,[4,6] Carlito B Lebrilla,[5,7] Kenneth Maleta,[4] Elizabeth L Prado,[1] John Sadalaki,[4] Sarah M Totten,[5] Lauren D Wu,[5] Angela M Zivkovic,[1,8] and Kathryn G Dewey[1]

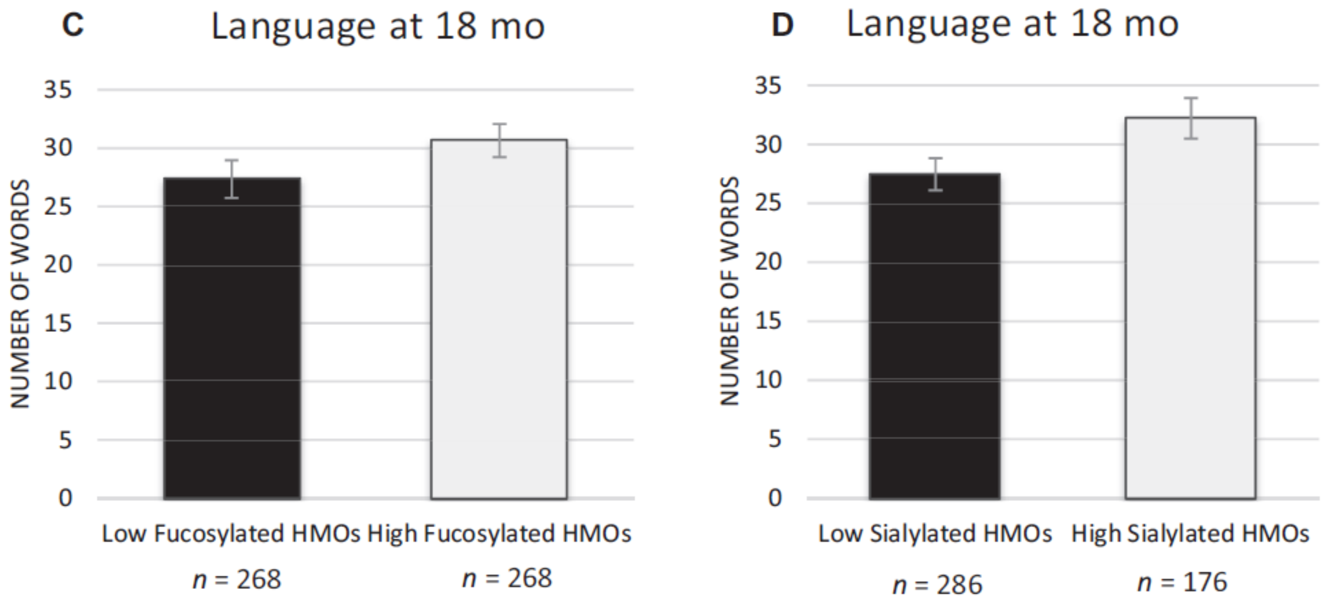
Am J Clin Nutr 2021;113:209–220.

Sialyllated and fucosylated HMOs are both associated with language development

Associations of human milk oligosaccharides and bioactive proteins with infant growth and development among Malawian mother-infant dyads

Josh M Jorgensen,[1] Rebecca Young,[1] Per Ashorn,[2,3] Ulla Ashorn,[2] David Chaima,[4] Jasmine CC Davis,[5] Elisha Goonat Chiza Kumwenda,[4,6] Carlito B Lebrilla,[5,7] Kenneth Maleta,[4] Elizabeth L Prado,[1] John Sadalaki,[4] Sarah M Totten,[5] Lauren D Wu,[5] Angela M Zivkovic,[1,8] and Kathryn G Dewey[1]

- Malawian mother-infant pairs (N = 869)
- Breast milk HMO content at 6 months of age
- A checklist based on the MacArthur–Bates Communicative Development Inventory used for language evaluation



Summary: HMOs and Brain Health

HMOs Support cognitive and language development

2’FL:	**Associated with better cognitive development** **Improves memory and learning[2]**	**Mother-Infant cohort study** **Pre-clinical trial**
3’SL:	**Associated with language development**	**Mother-Infant cohort study**
3’SL + 6’SL:	**Improves executive function and learning** **Role in cognitive function**	**Pre-clinical trial**
6’SL:	**Improves memory function[6]** **Improves attention and reduces impulsivity**	**Pre-clinical trial**

FL, fucosyllactose; SL, sialyllactose.

Key Messages

- There is rapid, dynamic and complex brain growth and development in the first years of life
- Genetic and environmental (nutrition) factors have been shown to modify this process
- Breastmilk, rich in nutrients such as HMOs is associated with improved brain development and cognition.
- Infants fed with HMOs supplemented formulae show comparable cognitive outcomes to breastfed infants.

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THANK YOU