Supporting Neurodevelopment With Brain-Building Nutrition

Presented by
John Colombo, PhD, *and*
Magnus Domellöf, MD, PhD

Pediatric Nutrition
CONTINUING EDUCATION FOR CLINICIANS

ANNENBERG CENTER FOR HEALTH SCIENCES
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This activity is supported by an educational grant from
Mead Johnson Nutrition.

Faculty Presenters

John Colombo, PhD

Professor of Psychology
Director, Schiefelbusch Institute for Life Span Studies
University of Kansas
Lawrence, Kansas

Magnus Domellöf, MD, PhD

Professor of Pediatrics
Umeå University
Senior Consultant (attending) Physician
Department of Clinical Sciences
Umeå, Sweden

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Learning Objectives

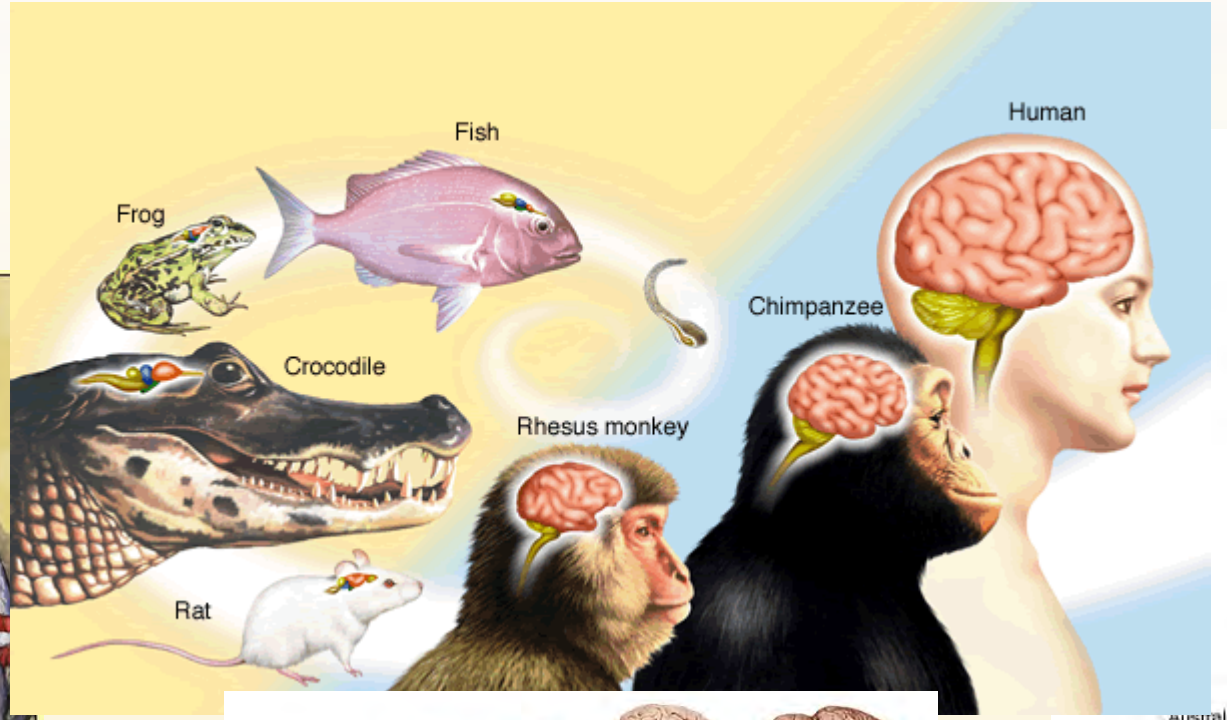
By participating in this education, you will better:

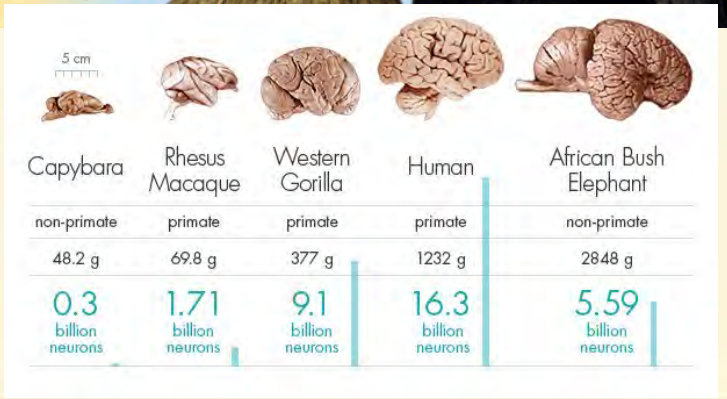
- Recognize the impact of nutrition on brain growth and neurodevelopment
- Identify key components of the structure, composition, and functionality of MFGM in breast milk and its significance to infant nutrition
- Support clinicians' confidence in their ability to communicate the clinical benefits of infant formula with MFGM in early infant growth and development

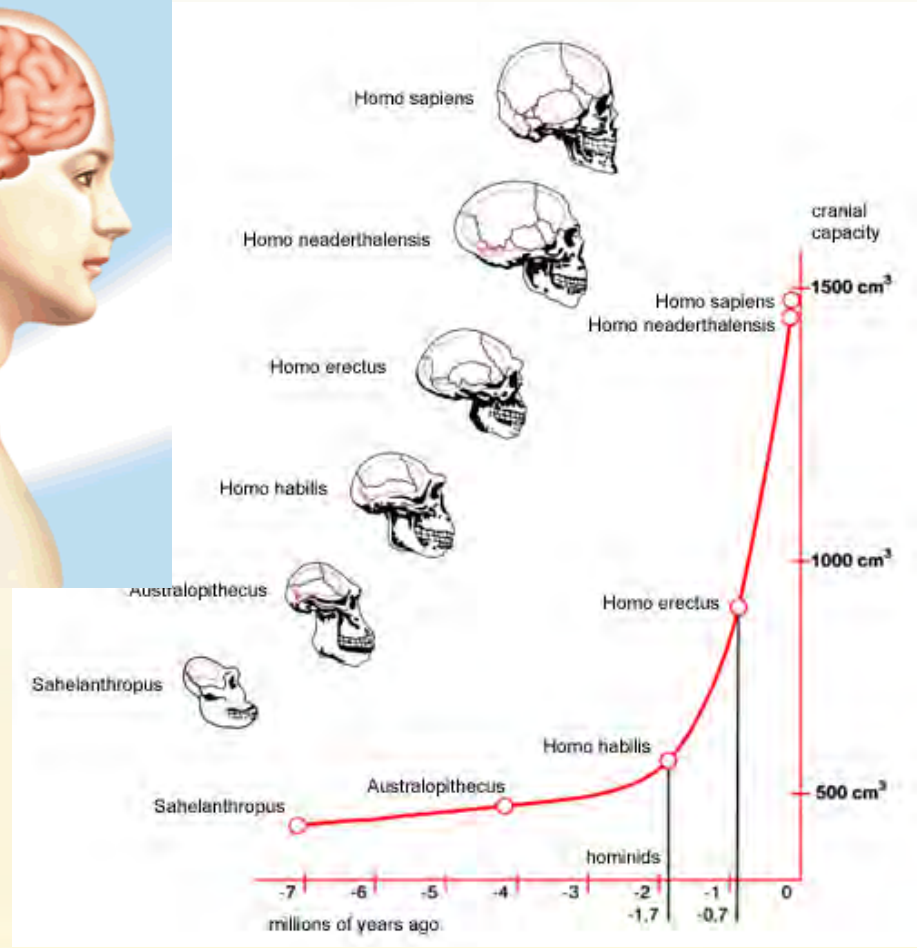
The First 1,000 Days: a Critical Period of Growth and Development

Magnus Domellöf, MD, PhD

Humans Have Big Brains



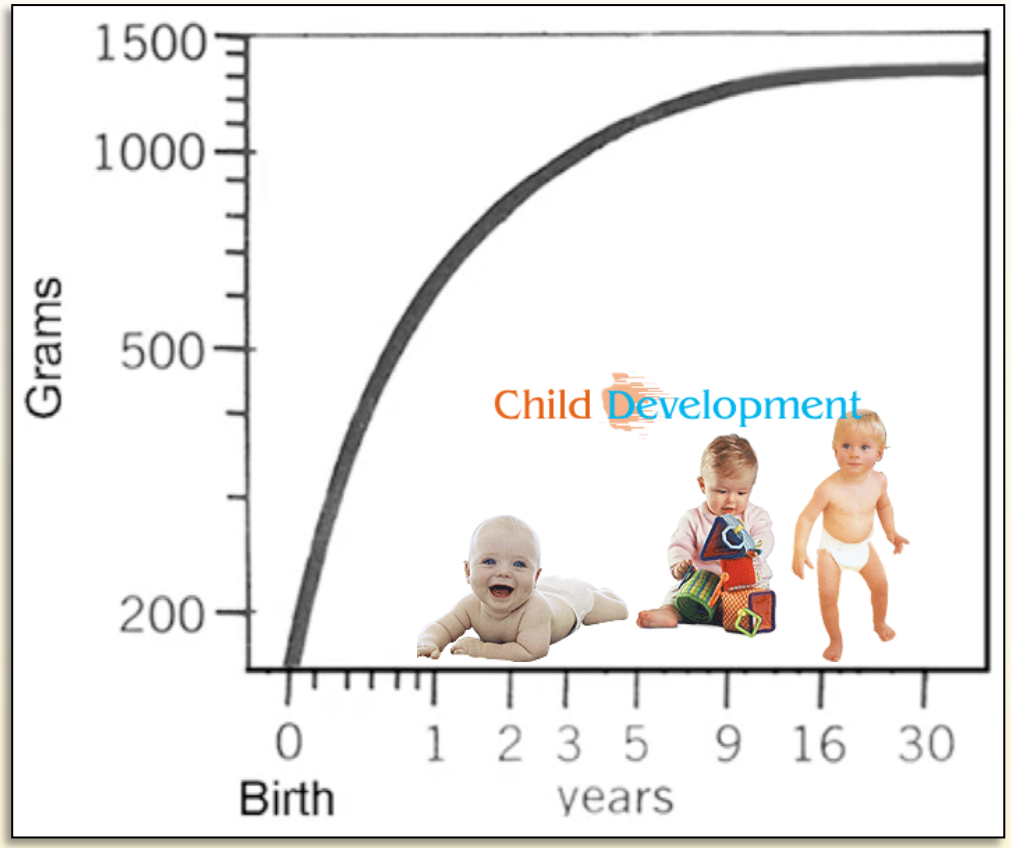




Dobbing J, Sands J. *Early Hum Dev.* 1979;3(1):79-83.

Brain Growth Spurt[1]

Brain Growth Velocity[2]

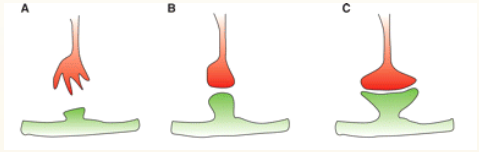


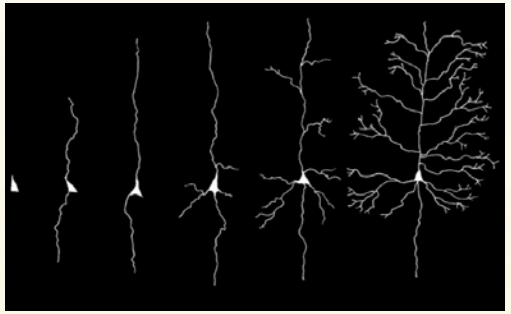
The brain is the fastest-growing organ in infants and toddlers.[2]

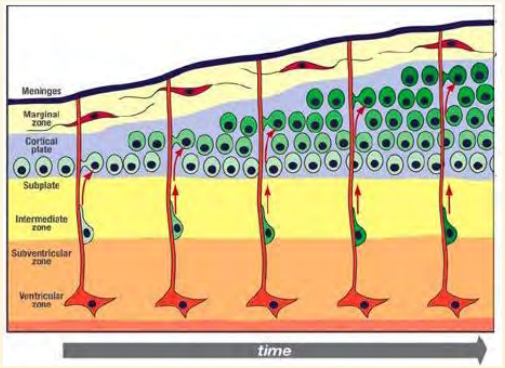
Age	Average weight
Birth	400 g
3 years	1200 g
Adult	1400 g

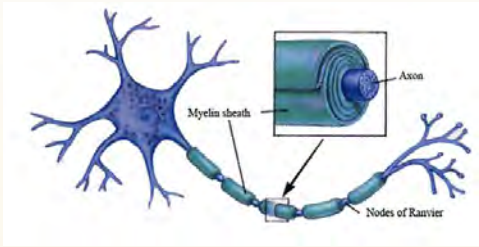
[1]. Dobbing J, Sands J. *Early Hum Dev*. 1979;3(1):79-83. [2]. University of Utah. Updated May 2020. https://neurologicexam.med.utah.edu/pediatric/html/dev_anatomy.html.

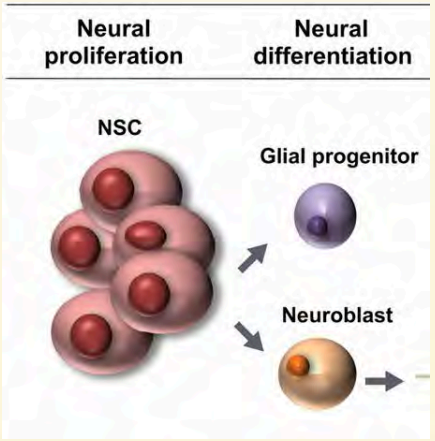
The First 1,000 Days: Extremely Important for Brain Development

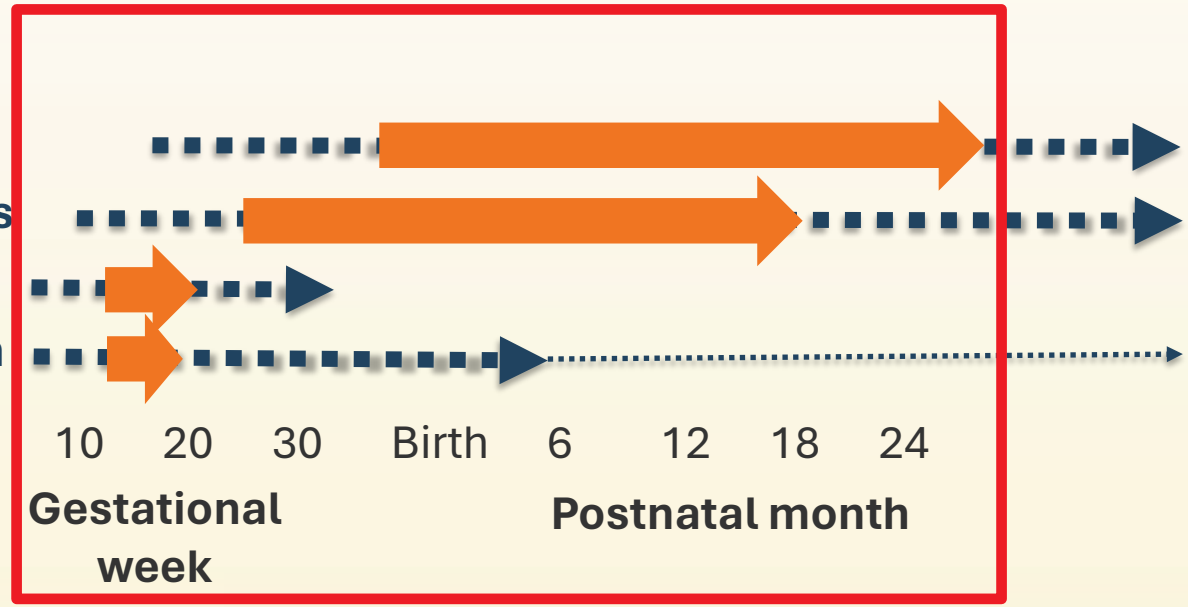










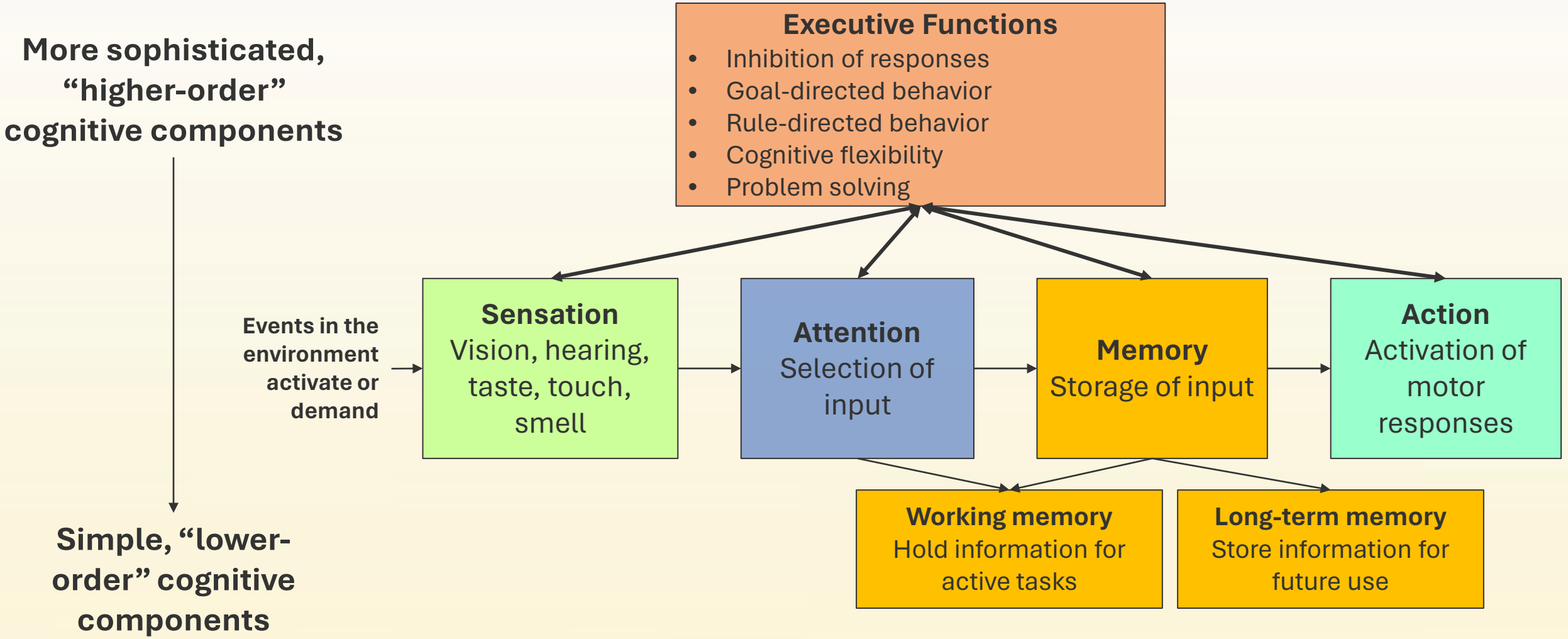


[1]. Save the Children Fund. Food for Thought. 2013. https://www.savethechildren.org.uk/content/dam/global/reports/hunger-and-livelihoods/food-for-thought.pdf. [2]. Gilmore JH et al. N*at Rev Neurosci*. 2018;19(3):123-137. [3]. Shankle WR et al. *Pediatr Dev Pathol*. 1999;2(3):244-259. [4]. Zhao X et al. *Front Hum Neurosci*. 2021;15:616132.

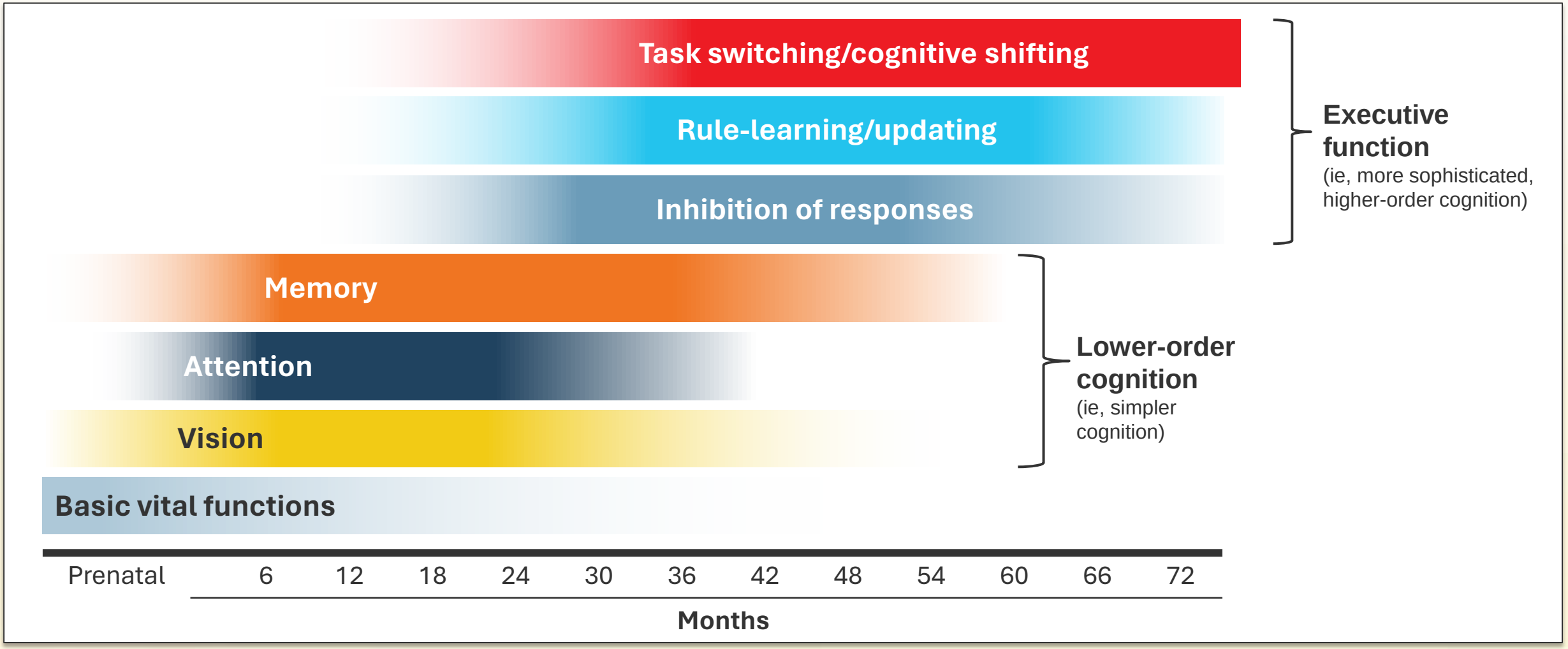
Assessing and Measuring Developmental Outcomes

John Colombo, PhD

Specific Cognitive Functions



Developmental Course of Cognitive Functions



Clinical Trial Outcomes to Measure Brain Development

When designing a clinical trial, identifying outcomes to effectively evaluate the treatment is critical.

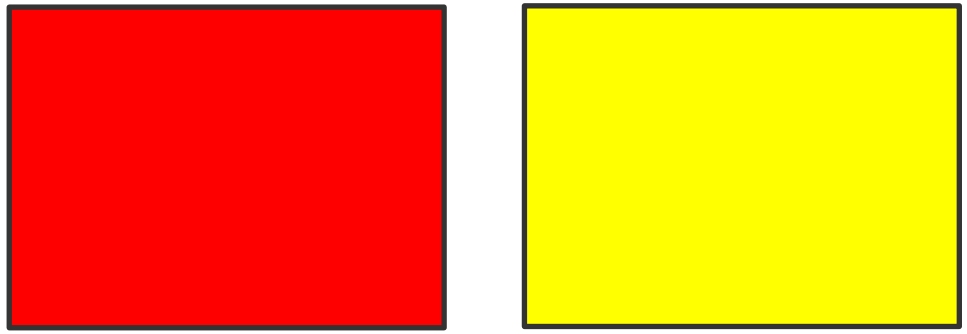
Options for measuring neurodevelopment include:

- Screening assessments
- Parent report measures (questionnaires)
- Standardized global developmental measures
- Tests of specific cognitive skills

Measuring Executive Function: Modified Stroop Task[1],[2]

- **Test:** asks children to respond to a stimulus based on a nonintuitive rule
- **Cognitive process measured:** inhibitory control, rule-learning and strategy, and working memory
- **Age group:** ≥30 months

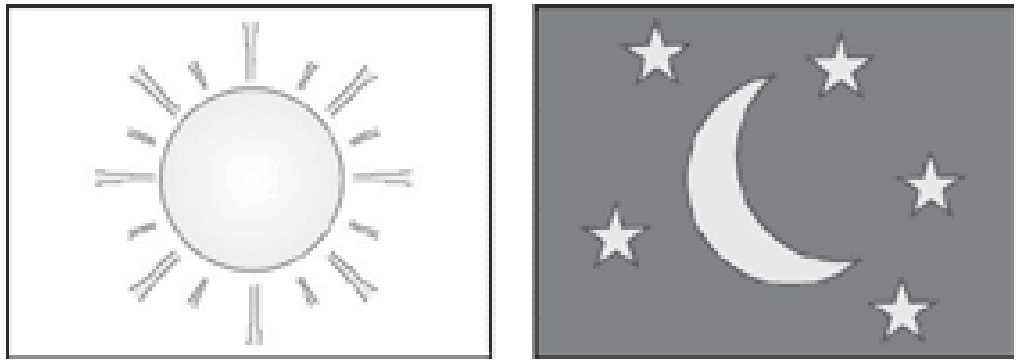
Color Task Variant



"Yellow"
(or "Banana")

"Red"
(or "Apple")

Day/Night Task Variant



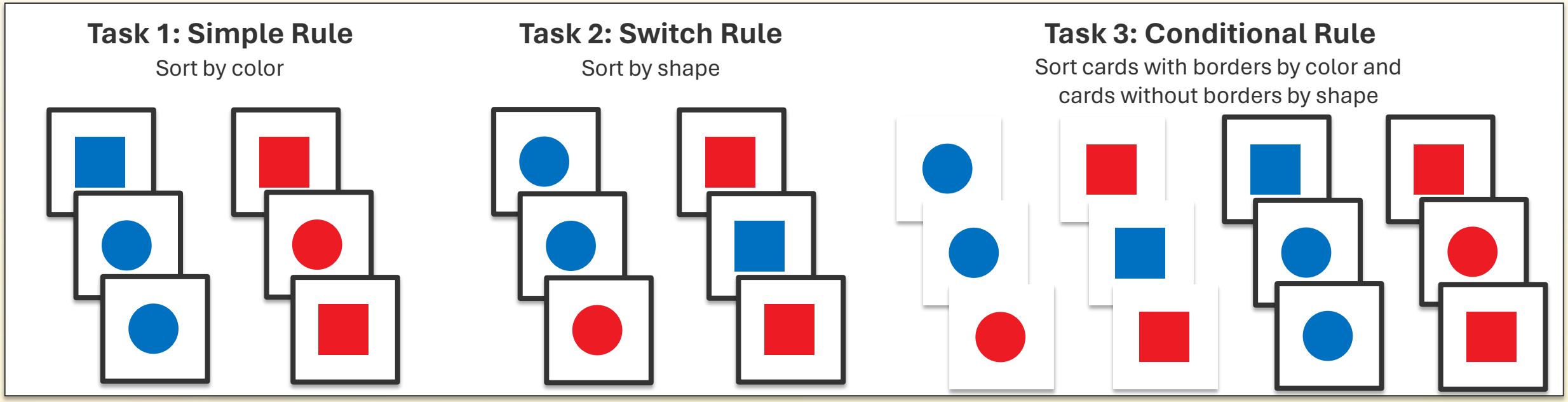
"Night"

"Day"

[1]. Colombo J et al. *Am J Clin Nutr*. 2019;109(5):1380-1392. [2]. Colombo J et al. *J Pediatr*. 2023;261:113483.

Measuring Executive Function: Dimensional Change Card Sort (DCCS) Task[1]-[3]

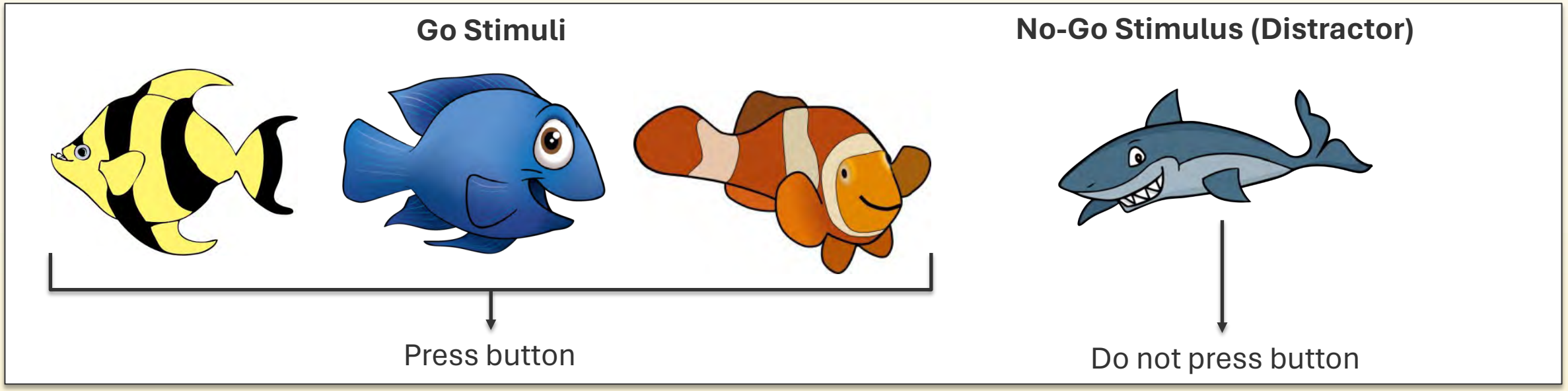
- **Test:** asks children to sort cards into boxes based on a specific characteristic (eg, color) and then asks them to *switch* and sort cards based on a different characteristic (eg, shape) and then again based on a conditional rule
- **Cognitive process measured:** rule-learning and cognitive flexibility
- **Age group:** ≥30 months



[1]. Colombo J et al. *Am J Clin Nutr*. 2019;109(5):1380-1392. [2]. Colombo J et al. *J Pediatr*. 2023;261:113483. [3]. Zelazo PD. *Nat Protoc*. 2006;1(1):297-301.

Measuring Executive Function: Go/No-Go Task

- **Test:** asks children to perform a quick motor response when specific stimuli are displayed (ie, “go” stimuli) and withhold this response for other stimuli (ie, “no-go” stimuli or distractors); often used in conjunction with event-related brain potential (ERP) recording[1]
- **Measures:** inhibitory control[1]
- **Age group:** usually ≥60 months, but has been used in younger children with some success[2]



[1]. Meule A. *Front Psychol*. 2017;8:701. [2]. Holmboe K et al. *PLoS One*. 2021;16(12):e0260695.

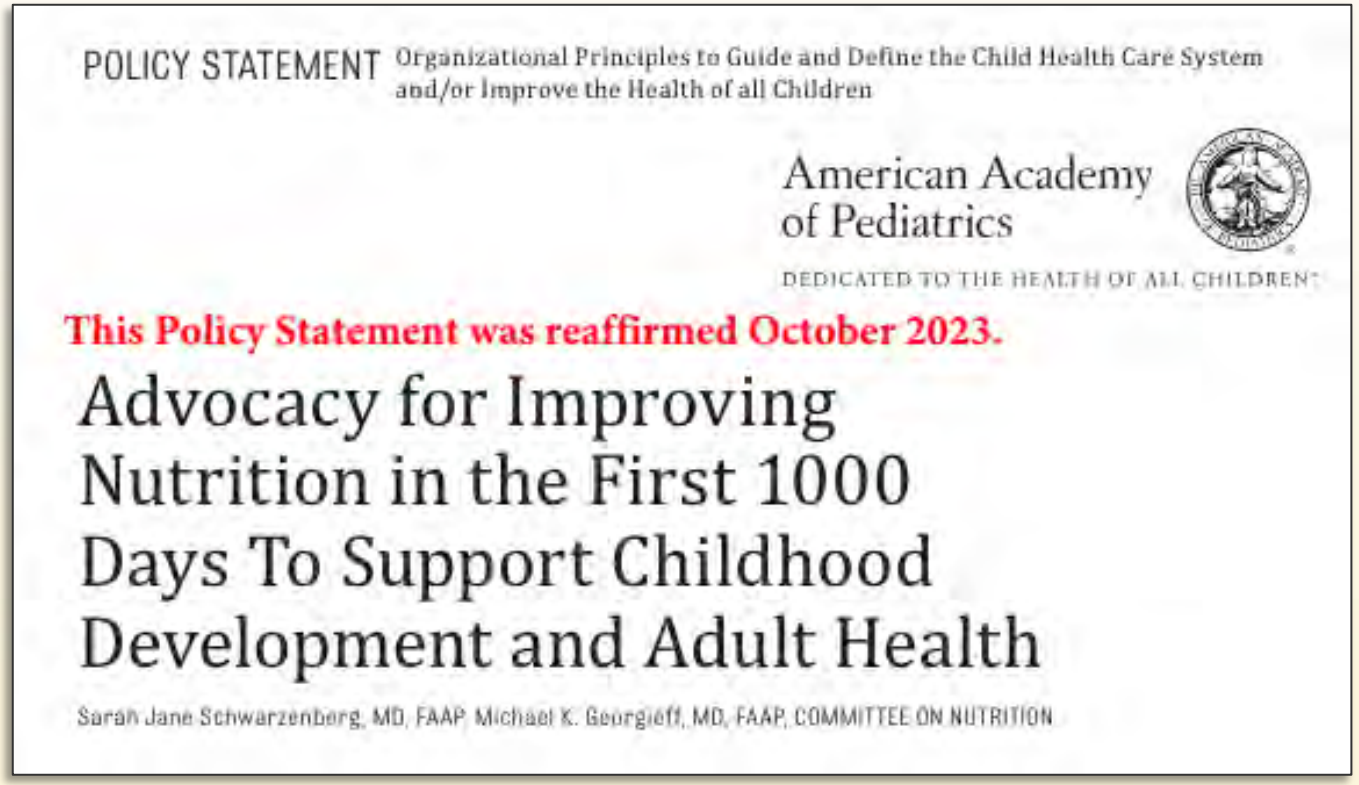
Human Milk: the Model for Optimal Early Nutrition

Magnus Domellöf, MD, PhD

Nutrition, Brain Development, and the Role of Clinicians

- The **American Academy of Pediatrics (AAP)** advocates for improving nutrition during the first 1000 days to support optimal development

- Optimizing nutrition requires an understanding of the “complex interplay” of the various nutrients that contribute to brain development



POLICY STATEMENT Organizational Principles to Guide and Define the Child Health Care System and/or Improve the Health of all Children

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™

This Policy Statement was reaffirmed October 2023.

Advocacy for Improving Nutrition in the First 1000 Days To Support Childhood Development and Adult Health

Sarah Jane Schwarzenberg, MD, FAAP, Michael K. Georgieff, MD, FAAP, COMMITTEE ON NUTRITION

Schwarzenberg SJ et al. *Pediatrics*. 2018;141(2):e20173716.

Nutrition and Brain Development

	Proliferation	Migration	Arborization	Synapse formation	Myelination
Protein & energy	X	X	X	X	X
Fatty acids	X		X	X	X
Iron	X		X	X	X
Iodine	X	X	X	X	X
Zinc	X		X	X	
Choline	X			X	
B vitamins	X		X	X	X

[1]. Cormack BE et al. *Nutrients*. 2019;11(9):2019. [2]. Georgieff MK. *Am J Clin Nutr.* 2007;85(2):614S-620S. [3]. Costello SE et al. *Nutr Rev.* 2021;79(12):1293-1306.

Breastfeeding: the Gold Standard for Infant Nutrition

Health benefits of breastfeeding include:

- Reduced risk of **infections**
- Improved **brain development**

Meek JY et al. *Pediatrics*. 2022;150(1):e2022057988.
Image credit: VALUA VITALY via shutterstock

Breastfeeding and IQ

- Compared with formula-fed term infants, breastfed infants have **higher IQ scores** at (pre)school ages
  - Differences of about 3 to 5 points
- Causality of breastfeeding difficult to prove in observational studies…

Anderson JW et al. *Am J Clin Nutr.* 1999;70(4):525-535.
Image credit: George Hodan in public domain

Breastfeeding and IQ *(Continued)*

- Meta-analysis of 17 studies, adjusting for multiple confounders
  - Most studies from high-income countries
- Breastfed subjects achieved higher IQ
  - Mean difference, 3.4 points (95% CI, 2.3-4.6 points)
- Similar effects in large and small studies
- Still significant effect in studies controlling for maternal IQ
  - Mean difference, 2.6 points (95% CI, 1.2-4.0 points)

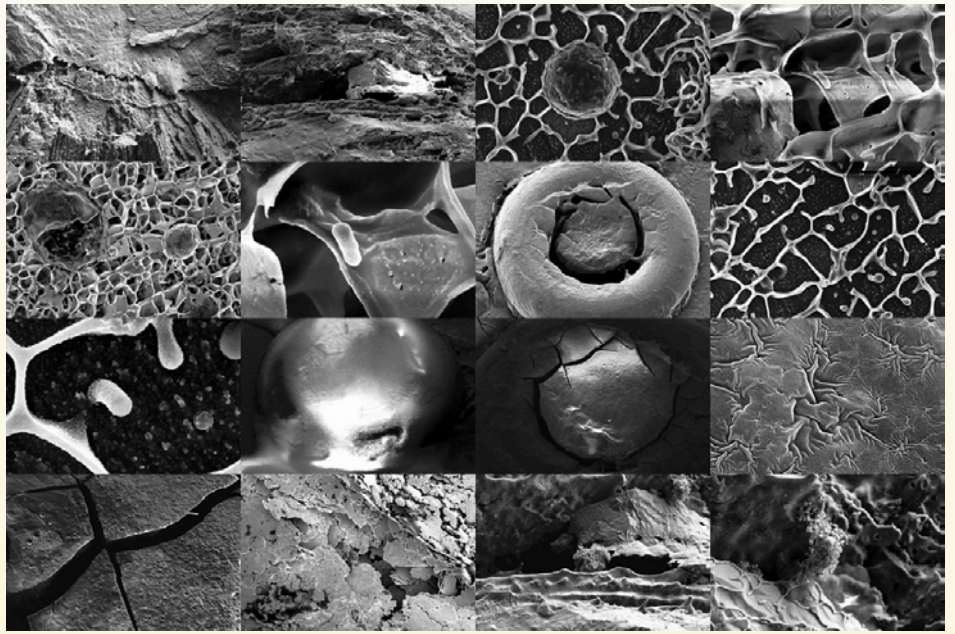
Differences in Cognitive Development Scores With Breastfeeding

	Number of studies	Mean difference (95% CI)	*P* value
Overall	18	3.44 (2.30; 4.58)	-
Age group			
1 to 9 years	13	4.12 (2.50; 5.73)	<.001
10 to 19 years	5	1.92 (0.43; 3.40)	.02
Study size			
<500	7	3.61 (1.59; 5.63)	<.001
≥500	11	3.36 (1.97; 4.74)	<.001
Control for maternal IQ			
No	9	4.10 (1.94; 6.25)	<.001
Yes	9	2.62 (1.25; 3.98)	<.001
Setting			
High income	16	3.65 (2.40; 4.90)	<.001
Middle/low income	2	1.88 (-0.07; 3.83)	.06
Categorization of breastfeeding			
Ever breastfed	7	3.62 (1.66; 5.59)	<.001
Breastfed for a given number of months	11	3.40 (1.73; 5.07)	<.001

Horta BL et al. *Acta Paediatr*. 2015;104(467):14-19.

Breast Milk Is a Highly Complex Biological Tissue

- Oligosaccharides
- Nonprotein nitrogen
- Nucleotides
- Complex lipids
- Growth factors
- Hormones
- Cytokines
- Bioactive peptides
- Enzymes
- Immunoglobulins
- Leucocytes
- Bacteria
- Exosomes
- Stem cells



de Weerth C et al. *Crit Rev Food Sci Nutr*. 2023;63(26):7945-7982.

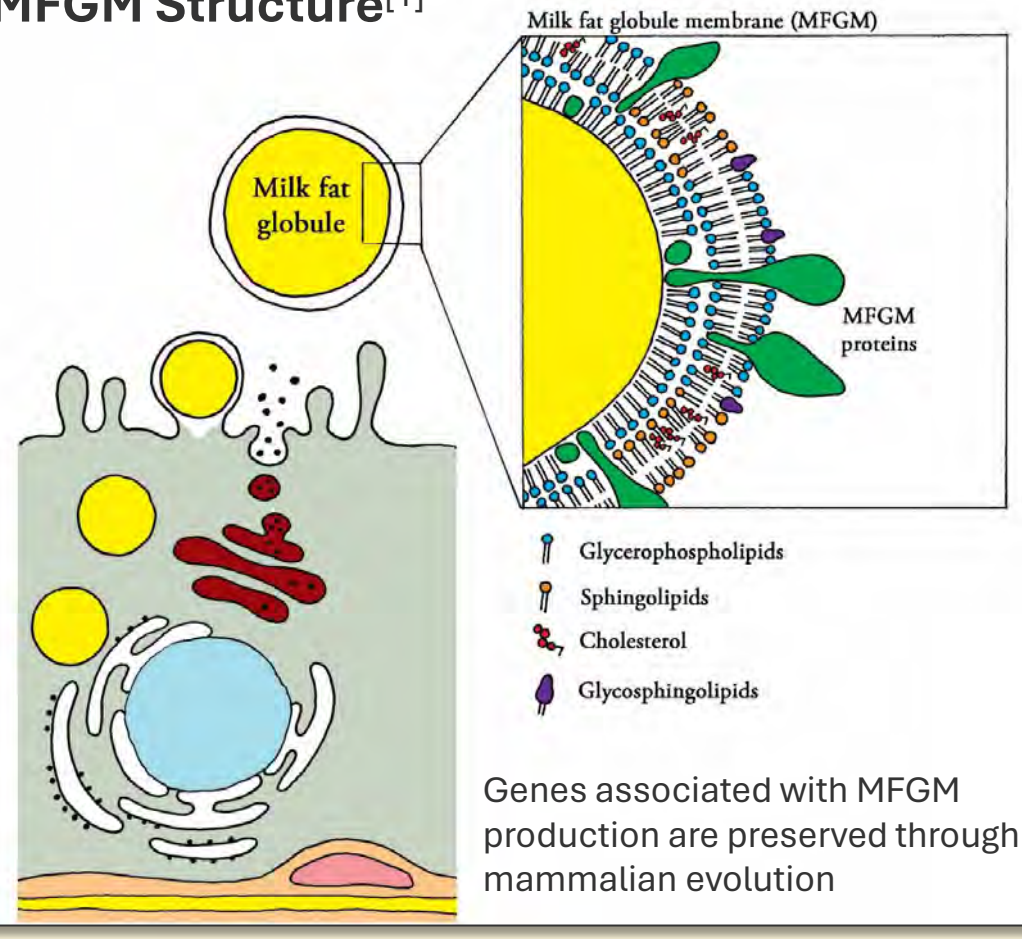
Bioactive Components of Breast Milk

- Components having a health effect beyond their purely nutritional contribution (eg, energy and macronutrient intakes)
- Bioactive components may improve immune function, promote neurodevelopment, and/or prevent morbidities

Ballard O, Morrow AL. *Pediatr Clin North Am*. 2013;60(1):49-74.

Milk Fat Globule Membrane (MFGM)

MFGM Structure[1]



Genes associated with MFGM production are preserved through mammalian evolution

Brain Function[2]

- **Choline**
- **Sphingomyelin**
- **Gangliosides**
- Cholesterol
- **Sialic acid**
- Inositol
- Cerebrosides

Immune Defense[2]

- **Mucins**
- **Butyrophilin**
- **Lactadherin**
- CD14
- TLR1
- TLR4
- Xanthine oxidase

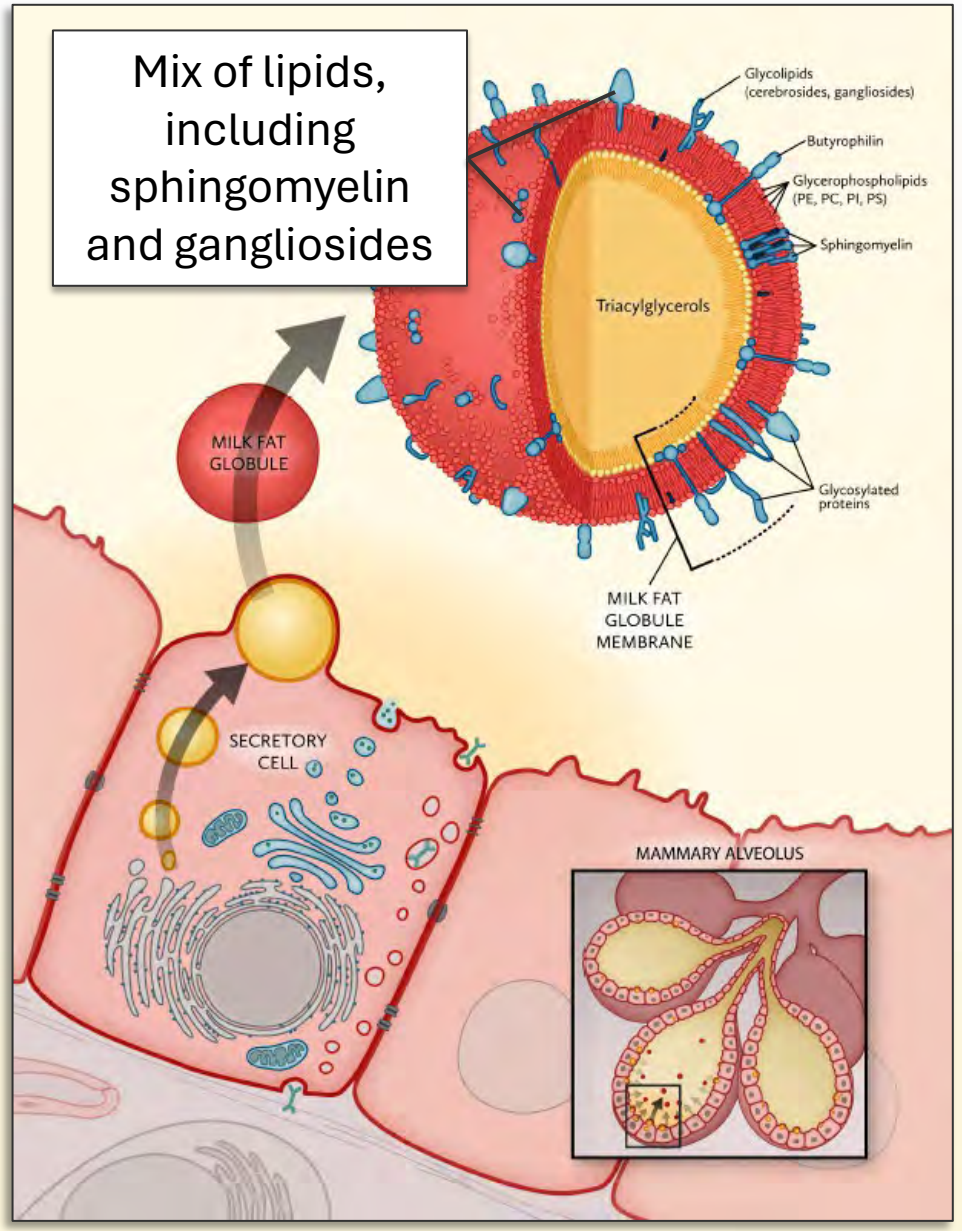
[1]. Hernell O et al. *J Pediatr.* 2016;173 Suppl:S60-S65. Illustration by Erik Domellöf. [2]. Timby N et al. *Adv Nutr.* 2017;8(2):351-355.

MFGM: Structure and Functions

John Colombo, PhD

Milk Fat Globule Membrane (MFGM) Overview

- Three-layer membrane of polar lipids, glycolipids, and proteins
- Surrounds triacylglycerol-rich milk fat globules
- Secreted by mammalian epithelial cells through exocytosis



Nie C et al. *Nutrients*. 2024;16(5):587.

Potential Impact of MFGM Supplementation on the Brain-Immune-Gut Axis and Neurodevelopment

Sphingomyelin and **glycosphingolipids (gangliosides)** are highly concentrated in the brain, contributing to synaptogenesis and myelination.[2]

Brain[1]

- Improved cognitive scores
- Improved developmental and attention scores
- Improved social and emotional behavior scores
- Improved short-term memory
- Fewer behavioral and affective disorders

Immune[1]

- Reduced risk of otitis media
- Fewer upper respiratory infection, cough, and diarrhea cases
- Lower levels of IL-2 and IL-17A
- Cytokine profile more similar to breastfed infants

Gut[1]

- Fewer incidences of diarrhea
- Fewer incidences of bloody diarrhea

Microbiome[1]

- Improved gut microbial activity and function
- Lower prevalence of otitis media–related bacteria

[1]. Mohamed HJJ et al. *JGH Open*. 2022;6(7):454-461. [2]. Hussain G et al. *Lipids Health Dis*. 2019;18(1):26.

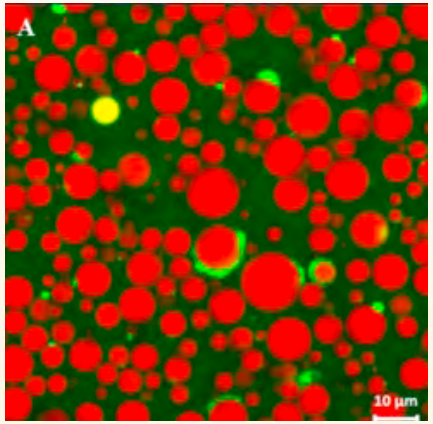
Potential Benefits of *MFGM* Supplementation in Infant Formula

John Colombo, PhD

Differences Between Lipids in Human Milk and Standard Infant Formula

Confocal Microscopy Images of Fat Droplets Showing Lipids (Red) and Proteins (Green)[1]

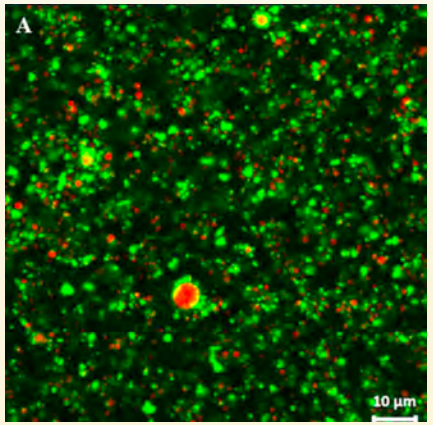
Human milk



Characteristics of Human Milk Fat Droplets[2]

- High sphingomyelin content
- Dynamic across lactation stages
- Large fat globules (~5 µm)
- Phospholipid bilayer membrane

Standard infant formula



Characteristics of Standard Infant Formula Fat Droplets[2]

- High phospholipid content
- High phosphatidylcholine content
- Small fat globules (~0.2 µm)
- No phospholipid bilayer membrane

[1]. Gallier S et al. *Colloids Surf B Biointerfaces*. 2015;136:329-339. Images used under a Creative Commons license (CC BY). © 2015, the Authors.
[2]. Wei W et al. *J Agric Food Chem*. 2019;67(50):13922-13928.

Studying the Benefits of MFGM Supplementation of Infant Formula: the Lighthouse MFGM Clinical Trial

- **Study design**
  - Prospective double-blind randomized controlled trial (RCT)
  - Enrolled **451 infants** and randomly assigned to 12 months of feeding with:
    - » Standard cow's milk-based formula (control)
    - » Standard cow's milk-based formula with added bovine MFGM (5 g/L) and lactoferrin (0.6 g/L) (MFGM+LF)
- **Primary outcome:** difference in Bayley Scales of Infant Development, 3rd edition (Bayley-III) cognitive composite scores at 12 months
- **Secondary outcomes:** tolerability/safety, growth/anthropometrics, and other measures of development

Li F et al. *J Pediatr*. 2019;215:24-31.e8.

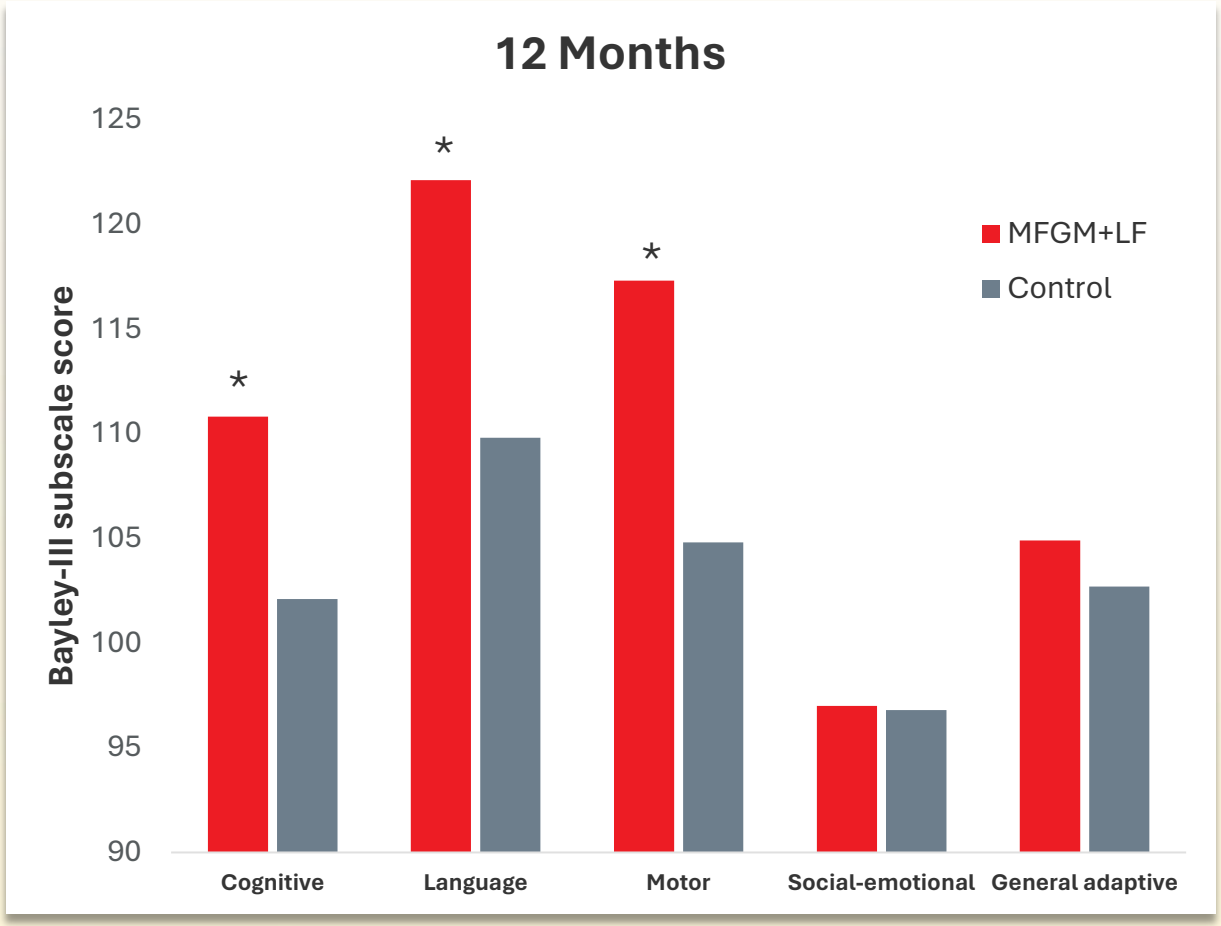
The Lighthouse MFGM Clinical Trial: Ages and Stages Questionnaire Outcomes

ASQ Domain Scores (Repeated Measures Analysis), Mean ± SE

Domains	Day 120		Day 180		Day 275		*P* value for age*study group interaction	*P* value for study group
	Control (n = 187)	MFGM + LF (n = 187)	Control (n = 185)	MFGM + LF (n = 183)	Control (n = 167)	MFGM + LF (n = 166)		
Communication	49.1 ± 0.5	51.4 ± 0.5	50.8 ± 0.5	51.5 ± 0.5	51.5 ± 0.6	52.5 ± 0.6	.238	.010
Gross motor	49.7 ± 0.6	52.3 ± 0.6	48.6 ± 0.6	49.5 ± 0.6	46.2 ± 0.7	47.1 ± 0.7	.299	.010
Fine motor	46.6 ± 0.6	49.5 ± 0.6	52.0 ± 0.6	52.9 ± 0.6	53.4 ± 0.6	54.6 ± 0.6	.130	.002
Problem solving	49.7 ± 0.6	52.1 ± 0.6	49.5 ± 0.6	51.1 ± 0.6	51.9 ± 0.6	52.7 ± 0.6	.408	.003
Personal/social	46.5 ± 0.6	50.2 ± 0.6	47.1 ± 0.6	48.4 ± 0.6	50.0 ± 0.6	51.0 ± 0.6	.032	<.001

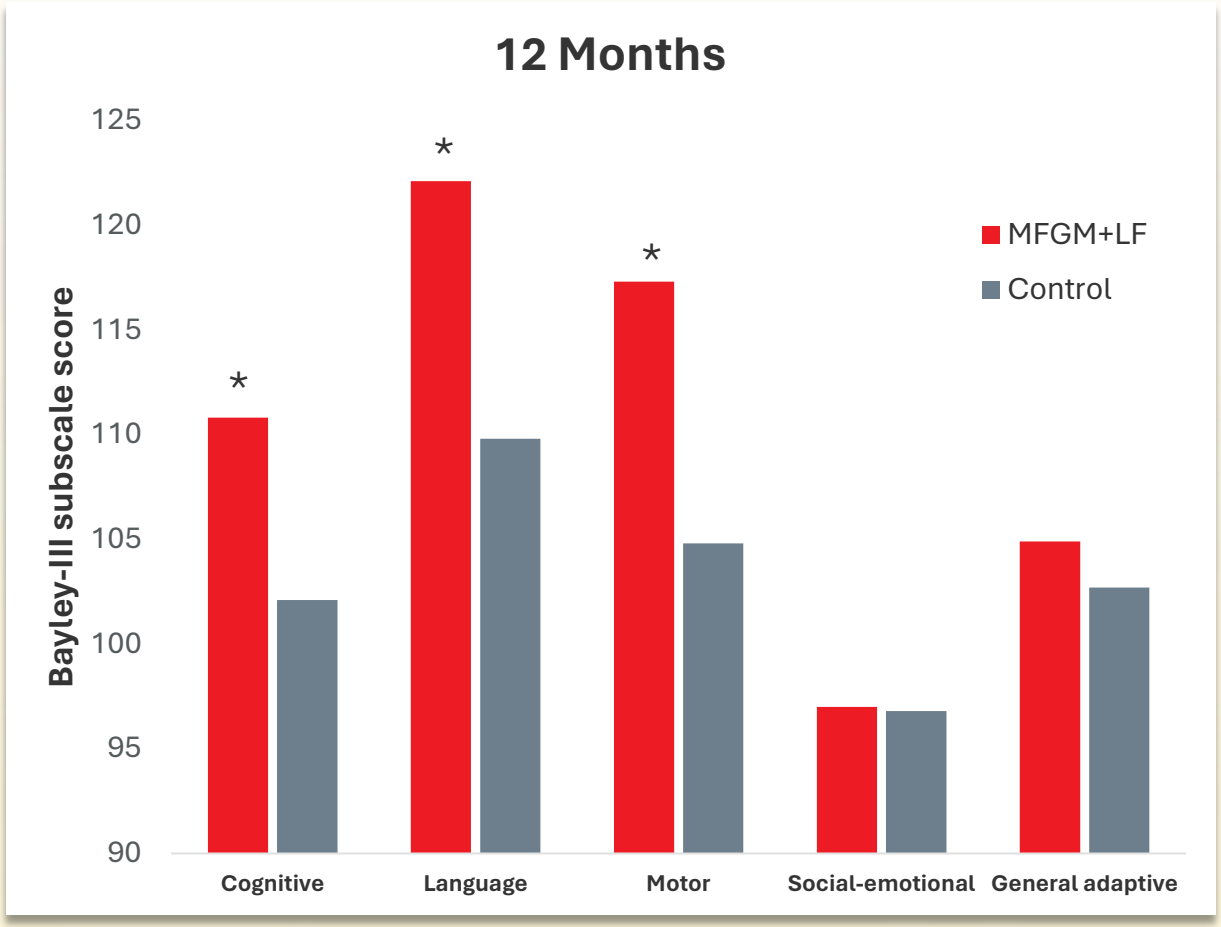
Li F et al. *J Pediatr*. 2019;215:24-31.e8.

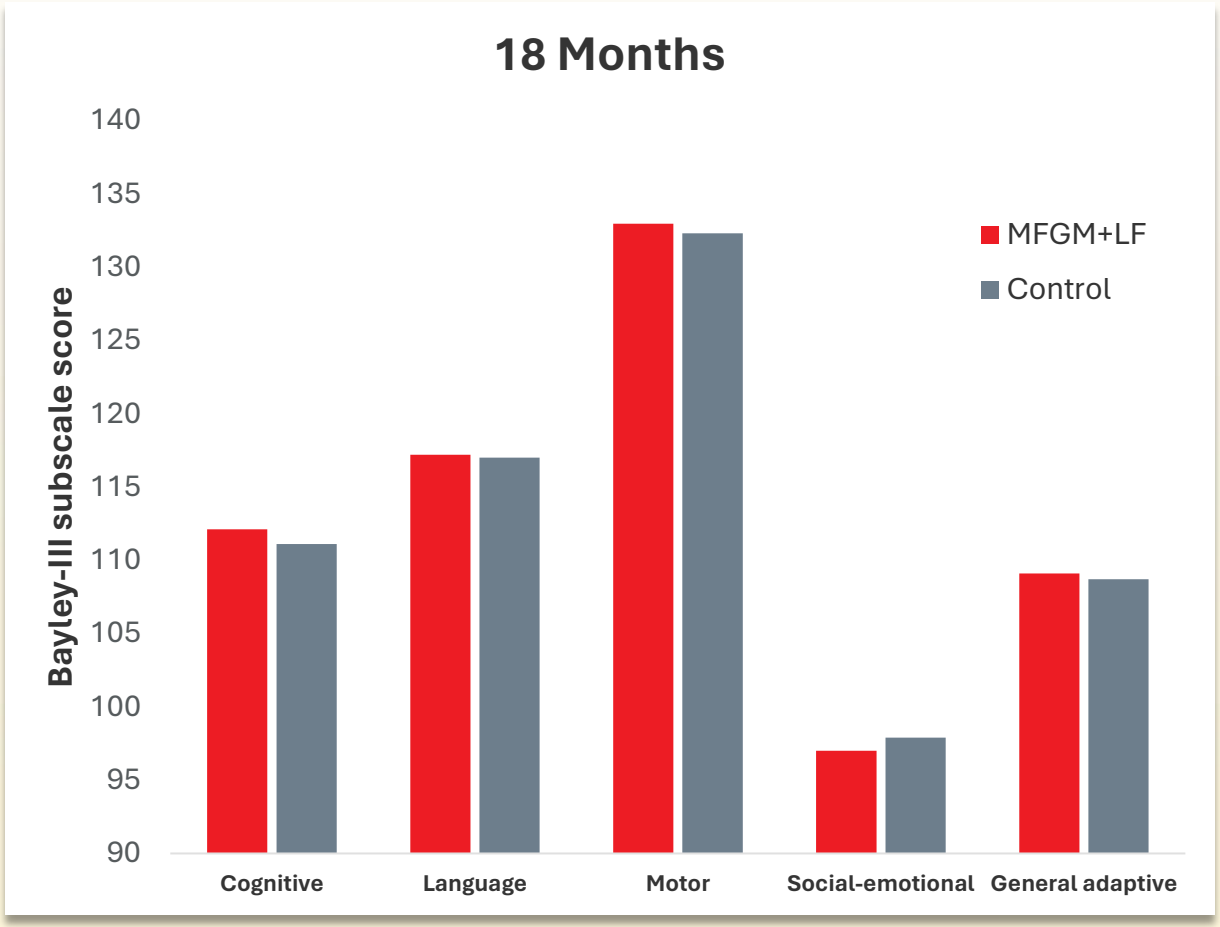
The Lighthouse MFGM Clinical Trial: Bayley-III Outcomes at 12 Months



*P <.001

The Lighthouse MFGM Clinical Trial: Bayley-III Outcomes at 18 Months





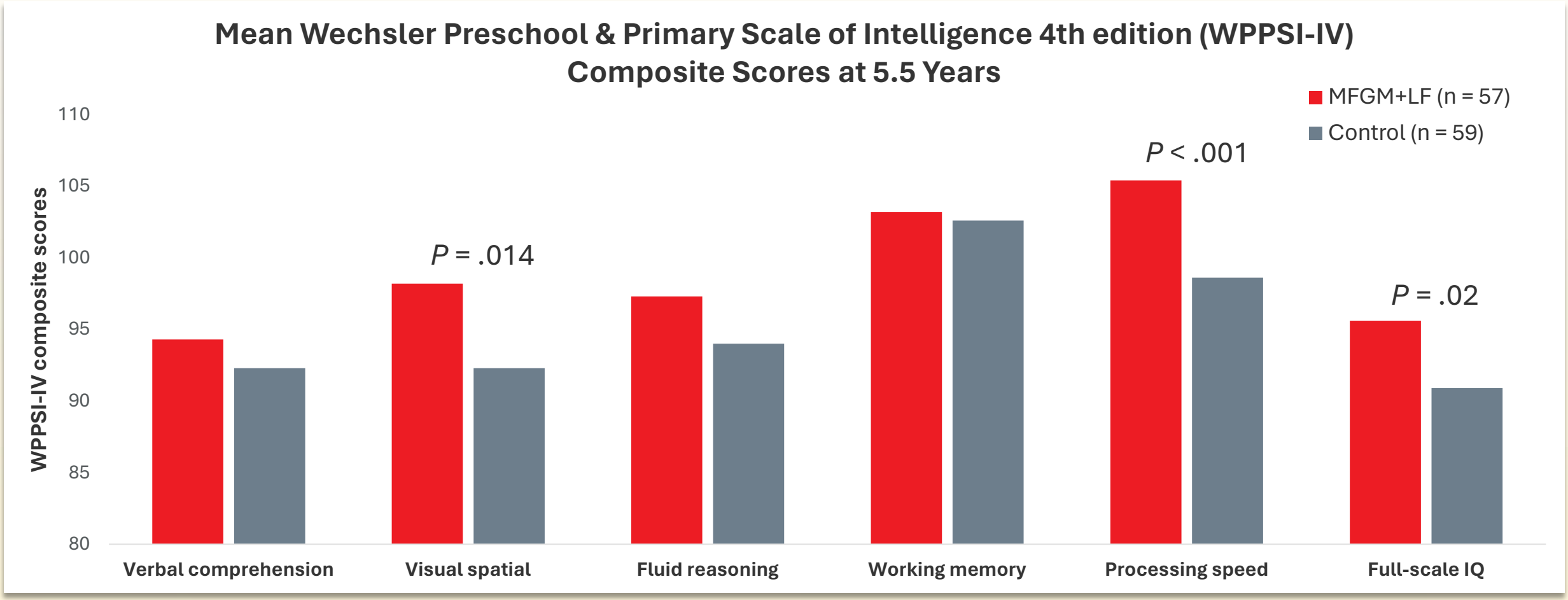
*P <.001

The Lighthouse MFGM Clinical Trial: Long-Term Follow-Up

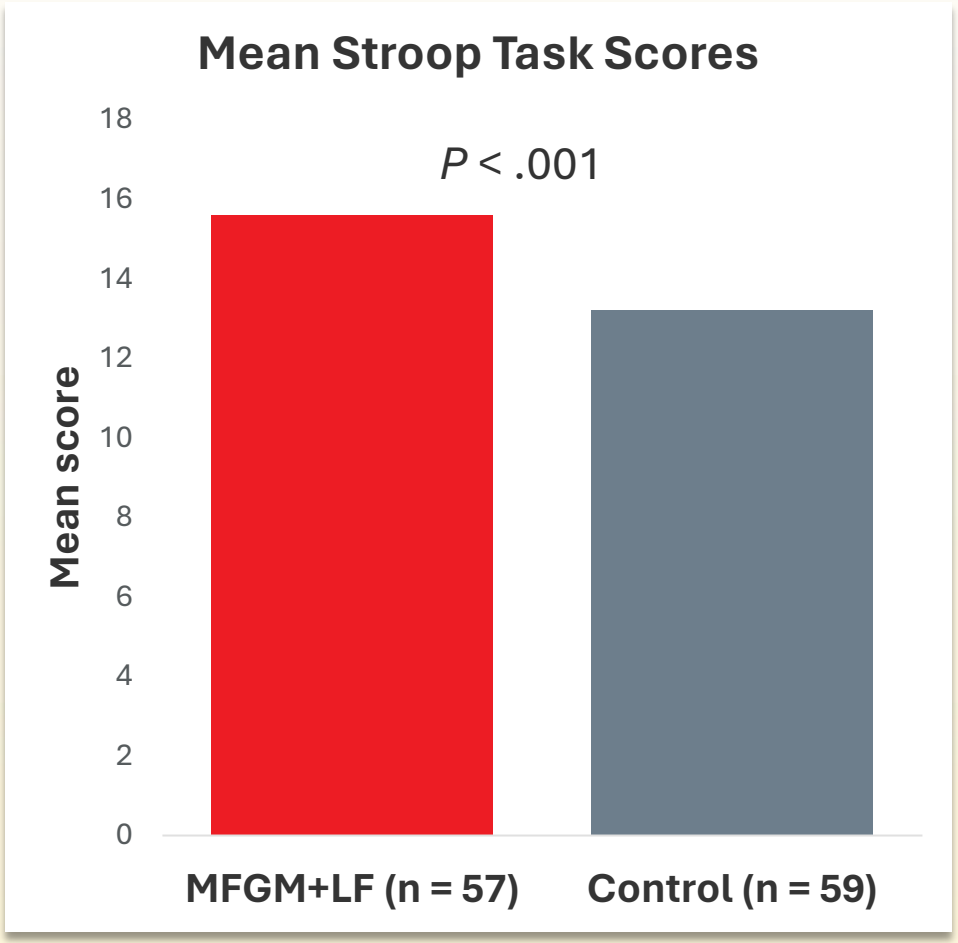
- **Follow-up study design**
  - Enrolled trial participants who completed 12 months of the assigned study feeding who were 5.5 years (±2 months) at the time of study testing
  - **116** of **292 participants** meeting eligibility criteria were enrolled
    - » No differences in demographic characteristics between those who did or did not participate in the follow-up study
- **Primary outcome measures**
  - WPPSI-IV Full-Scale IQ (a measure of overall intellectual ability)
  - 5 primary WPPSI-IV indices (measures of the domain-specific abilities of verbal comprehension, visual spatial, fluid reasoning, working memory, and processing speed)

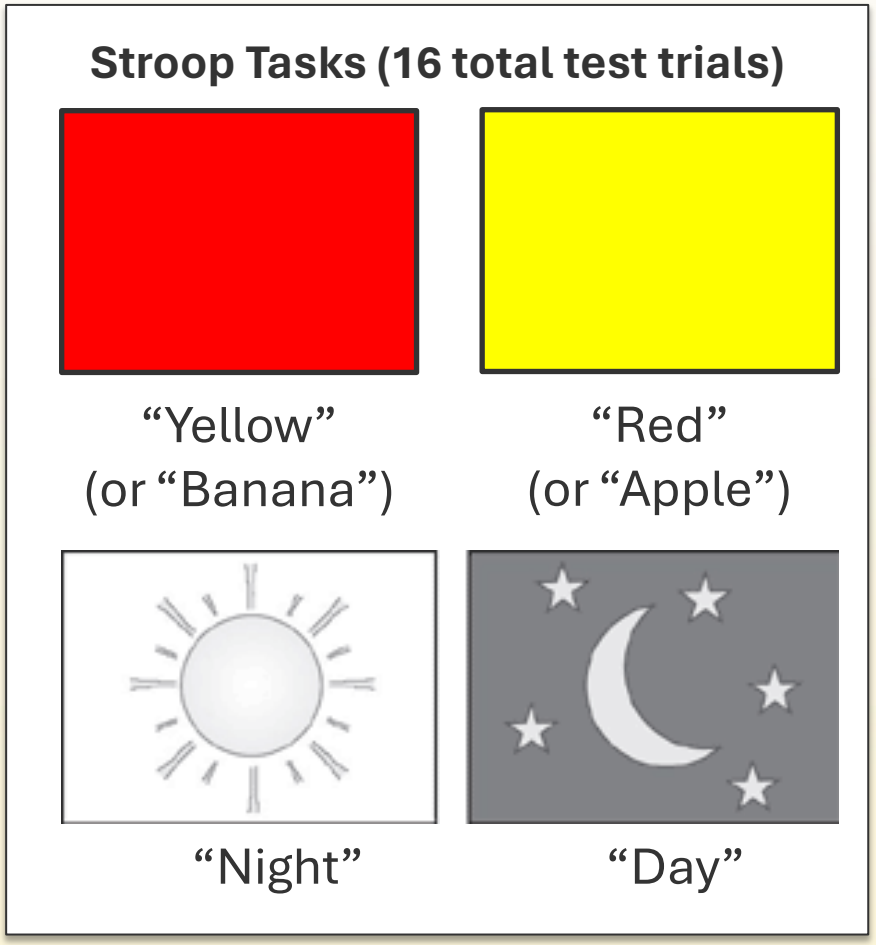
Colombo J et al. *J Pediatr*. 2023;261:113483.

The Lighthouse MFGM Clinical Trial Long-Term Follow-Up: Outcomes at 5.5 Years



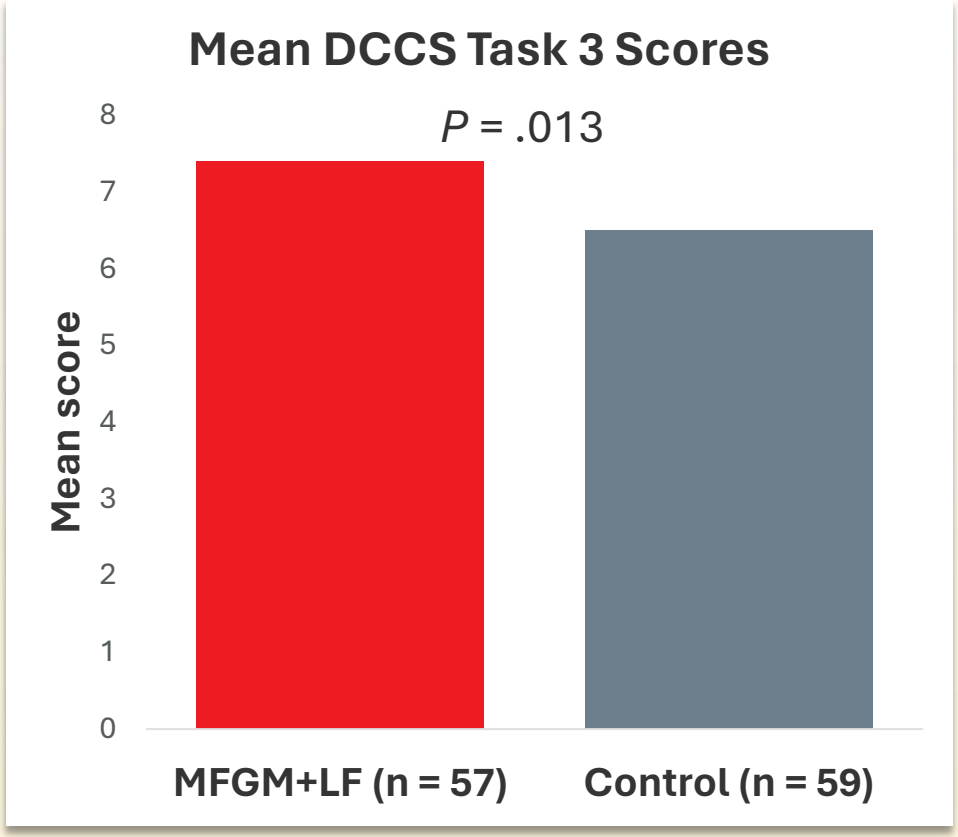
The Lighthouse MFGM Clinical Trial Long-Term Follow-Up: Stroop Task at 5.5 Years

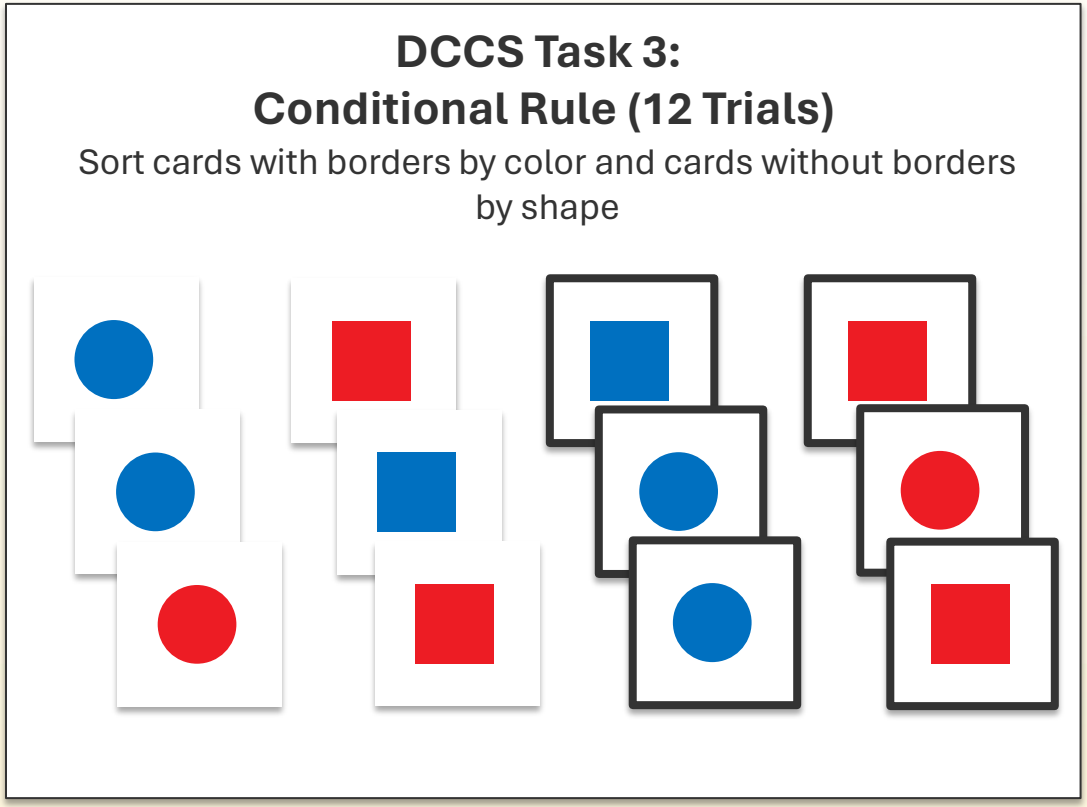




Colombo J et al. *J Pediatr*. 2023;261:113483.

The Lighthouse MFGM Clinical Trial Long-Term Follow-Up: DCCS Task at 5.5 Years





Note: There were no between-group differences in the DCCS task 1 (simple rule) or task 2 (switch rule) scores.

Other Potential Benefits of Supplementing Infant Formula With Bovine MFGM

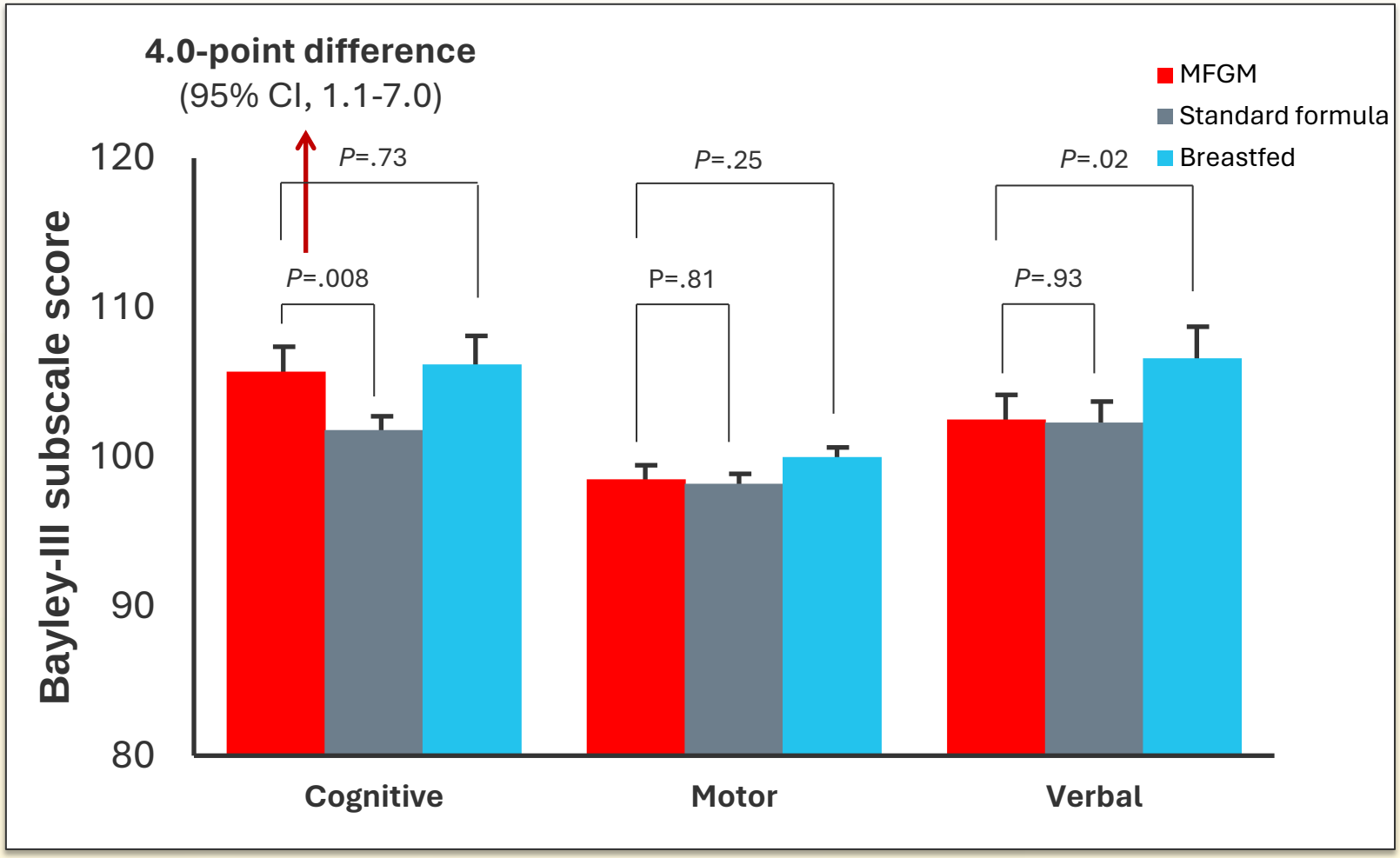
- Improvement in **adaptive behavior** at 12 months[1]
- Reduction in **infection** rates[2]
- Maintenance of **intestinal barrier** integrity[2]
- Modulation of the **gut microbiome**[3]

[1]. Xia Y et al. *Asia Pac J Clin Nutr*. 2021;30(3):401-414. [2]. Hernell O et al. *J Pediatr*. 2016;173 Suppl:S60-S65. [3]. Mohamed HJJ et al. *JGH Open*. 2022;6(7):454-461.

MFGM: Additional Data, Clinical Applications, and Ongoing Questions

Magnus Domellöf, MD, PhD

Swedish MFGM Study: Neurodevelopment at 12 Months



- Randomized, controlled study
- 160 healthy formula-fed infants were randomized to receive:
  - Standard formula until 6 months of age (n = 68)
  - Standard formula supplemented with MFGM (4% wt:wt) until 6 months of age (n = 73)
- A breastfed reference group was also recruited from the same hospital (n = 72)

Promising Results From Our Swedish MFGM Study

- **Improved cognitive scores** at 12 months[1]
- **Reduced infections** from 0–6 months, especially acute otitis media[2]
- **6-year follow-up**[3]
  - No remaining effects on neurodevelopment
  - No anthropometric or metabolic effects

[1]. Timby N et al. *Am J Clin Nutr*. 2014;99(4):860-868. [2]. Timby N et al. *J Pediatr Gastroenterol Nutr*. 2015;60(3):384-389. [3]. Timby N et al. *Am J Clin Nutr*. 2021;113(3):586-592.

RCTs of MFGM in Children (Published Since 2014)

Country	Age	N	Intervention formula	Primary outcome	Results	Ref
China	0–12 mo	212	MFGM	Safety and tolerance	Safe	Jiang, 2022
Chile	4–12 mo	347	MFGM	Growth and safety	Safe	Jaramillo-Ospina, 2022
USA	0–12 mo	373	MFGM, low iron, low protein	Growth and tolerance	Safe	Hedrick, 2021
China	0–5 mo	386	MFGM	Infections	No effect	Li X, 2019
China	0–12 mo	212	MFGM	Neurodevelopment	Partly positive	Xia, 2021
China	0–12 mo	451	MFGM + lactoferrin	Neurodevelopment	Very positive	Li F, 2019
Spain	1–18 mo	170	MFGM, LCPUFAs, oligosaccharides, sialic acid, gangliosides, nucleotides and probiotics	Neurodevelopment	Partly positive	Nieto-Ruiz, 2020

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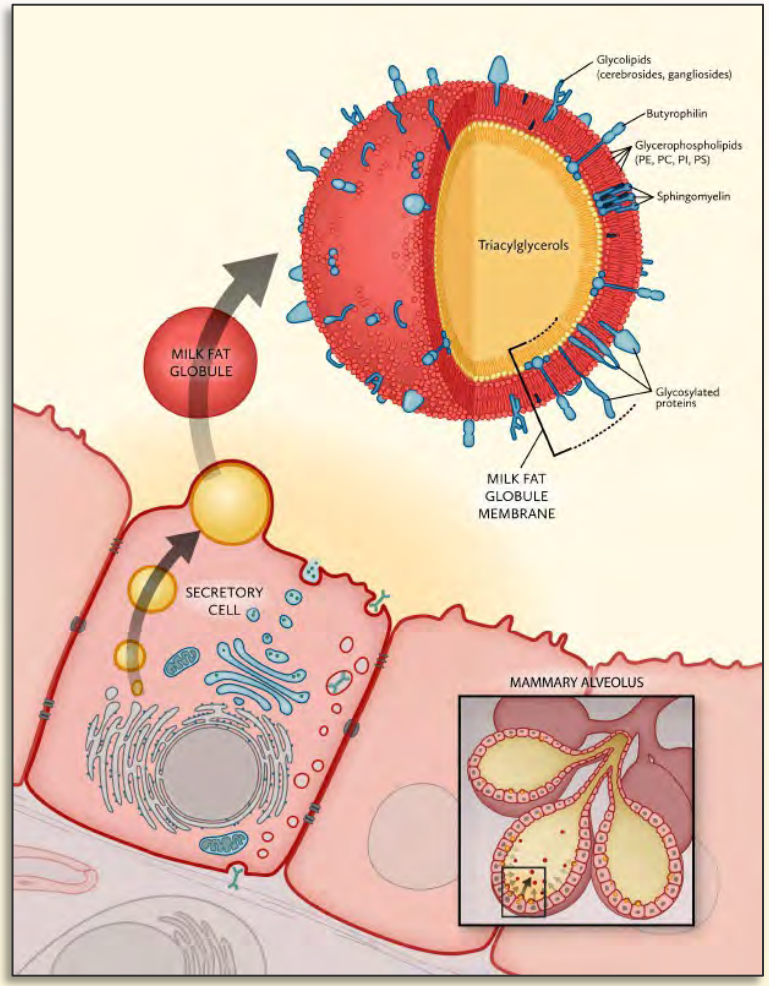
MFGM as a Supplement to Infant Formula Is Still Very Promising

- **Positive effect on neurodevelopment?**
  - 4 of 4 RCTs have shown some effect
  - 1 of 3 showed remaining effect at 5–6 years
- **Prevention of infections?**
  - 5 of 7 RCTs have shown some effect
  - Different interventions and outcomes and time periods
- **Remaining challenges:**
  - Different MFGM products with different lipids and protein composition
  - More high-quality RCTs with well-defined MFGM fractions are needed



Future Perspectives: Ongoing Questions

Would some at-risk groups of breastfed infants benefit from additional MFGM? For example:

- Preterm infants? (increased risk of cognitive impairment and infections)
- Infants with immune deficiency?
- Infants with acquired brain lesions?

Conclusions for Clinical Practice

- **Breastfeeding should be supported**
  - Ensures MFGM intake and best health outcomes
- **For those who cannot breastfeed, MFGM-supplemented infant formulas are available**
  - Safe, possible health benefits, but more studies are needed to prove the clinical effects of this intervention

Image credit: Oksana Shufrych via shutterstock

Key Takeaways

John Colombo, PhD
Magnus Domellöf, MD, PhD

Key Takeaways: Nutrition and Neurodevelopment in Infants

- The brain is the fastest-growing organ in infants and toddlers.
- According to the AAP, optimizing nutrition requires an understanding of the “complex interplay” of the various nutrients that contribute to brain development.
- Breastfeeding is the gold standard for infant nutrition and has been associated with improved neurodevelopment.

Key Takeaways: Bioactives and MFGM

- The bioactive components of breast milk may improve immune function, promote neurodevelopment, and/or prevent morbidities.
- MFGM is a 3-layer membrane of polar lipids, glycolipids, and proteins that surrounds triacylglycerol-rich milk fat globules in mammalian milk.
- Compared with infant formula fat droplets, human milk fat droplets are larger (~5 vs 0.2 μm) and have higher sphingomyelin contents.

Key Takeaways: MFGM Supplementation in Infant Formula

- In some randomized trials, MFGM supplementation in infant formula has been associated with improved cognitive outcomes.
- MFGM supplementation may also reduce the risk of infection, help maintain intestinal barrier integrity, and modulate the gut microbiome.
- For those who cannot breastfeed, MFGM-supplemented infant formulas are safe and may have health benefits—but more studies are needed on the clinical effects of MFGM supplementation.