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Exposure to Simple and Complex Carbohydrates in Human Milk and the Developing Infant Brain

March 7th, 2024

Lynne Ausman | Paige Berger

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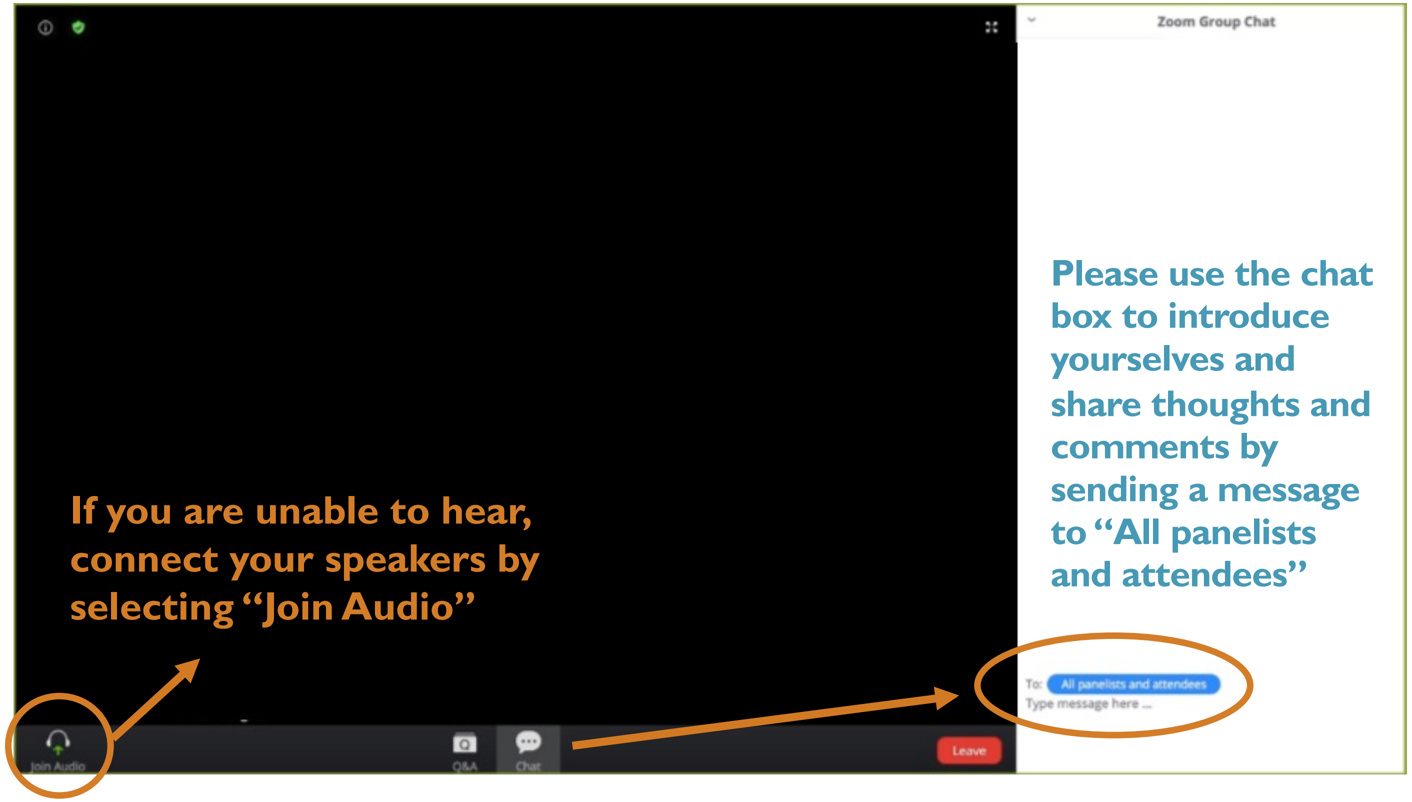
WELCOME TO THE ZOOM WEBINAR



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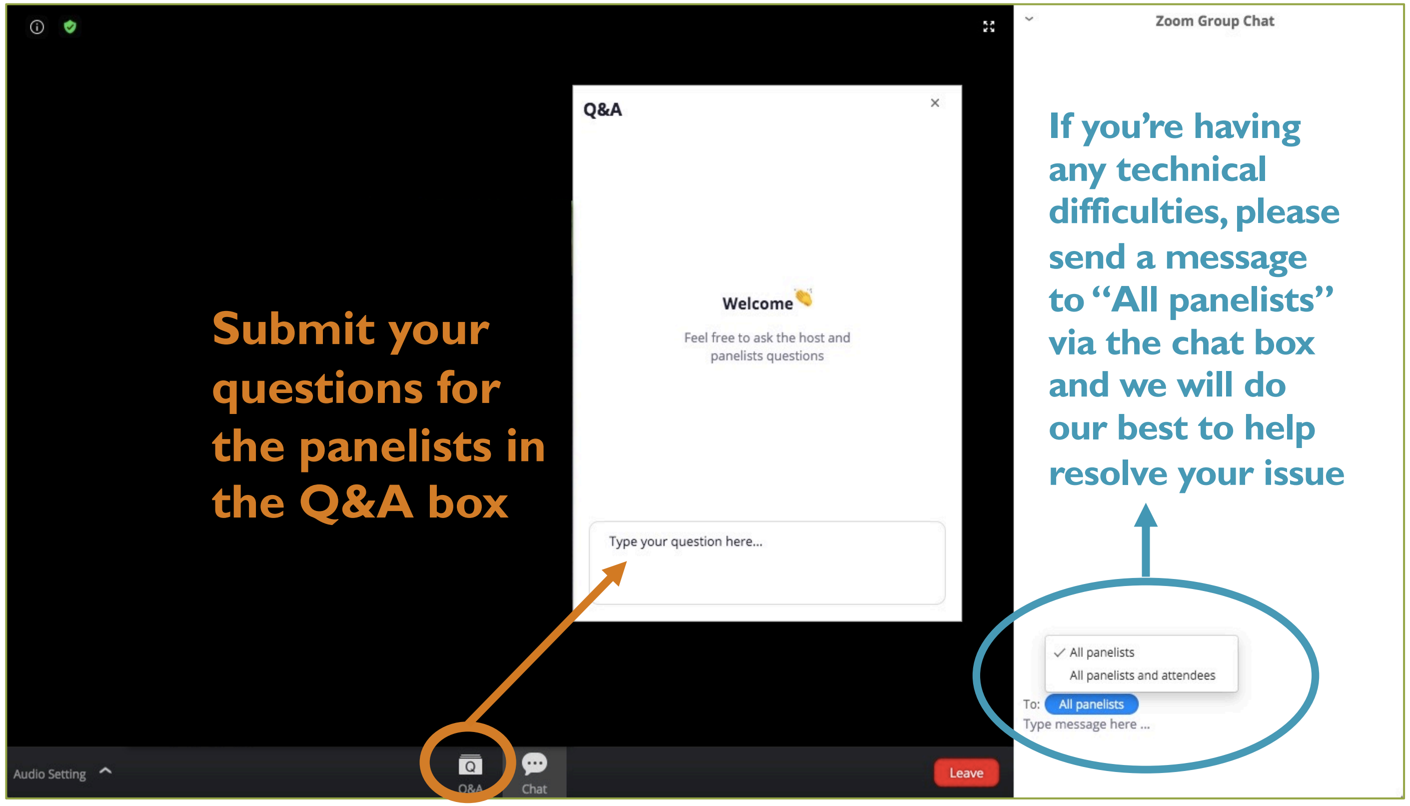
Q&A AND CHAT



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Jordan Nutrition Innovation Lab Webinar

Exposure to Simple and Complex Carbohydrates in Human Milk and the Developing Infant Brain

Thursday, March 7th, 2024
5:00-6:00 pm Jordan Time | 9:00-10:00 am US Eastern

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CARBOHYDRATES IN HUMAN MILK AND THE DEVELOPING INFANT BRAIN

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DISCLOSURES

- Dr. Berger receives research support from the National Institute of Child Health and Human Development and the Allen Foundation

- She was also invited to present her research findings during a session sponsored by the Abbott Nutrition Health Institute at the International Conference on Nutrition & Growth 2024

OBJECTIVES

Today, we will discuss the influence of carbohydrates in human milk on structural brain development and cognitive function in human milk-fed infants

At the end of this presentation, you will meet the following learning objectives:

1. Understand that human milk is a complex biological system with myriad components
2. Recognize that carbohydrates are the most abundant constituent of human milk
3. Understand role of maternal diet and genetics in determining carbohydrates in human milk
4. Describe state-of-the-science on specific human milk carbohydrates and developing infant brain

HUMAN MILK IS THE RECOMMENDED DIET FOR VIRTUALLY ALL INFANTS

Evidence of Benefits:

- Brain Maturation & Neurodevelopment
- Immune System Maturation & Reduced Infections
- Physical/Linear Growth & Reduced Obesity Risk
- Metabolic Health & Lower Diabetes Risk
- Self-Regulation of Intake & Better Appetite Control

Image credit: Adapted from https://www.parentmap.com/article/breastfeeding-pediatrician-new-mom-advice

TO WHAT EXTENT IS HUMAN MILK EXPOSURE BENEFICIAL FOR BRAIN?

Breastfeeding duration associated with improved cognitive development at school age and beyond

- Breastfeeding for >3 months associated with better communication and problem solving in infancy
- Greater duration of breastfeeding associated with higher IQ and educational attainment in adulthood

Yet, extent to which breastfeeding is beneficial for the brain remains a topic of discussion

- Strength of relationships between human milk exposure and cognitive outcomes varies from study to study

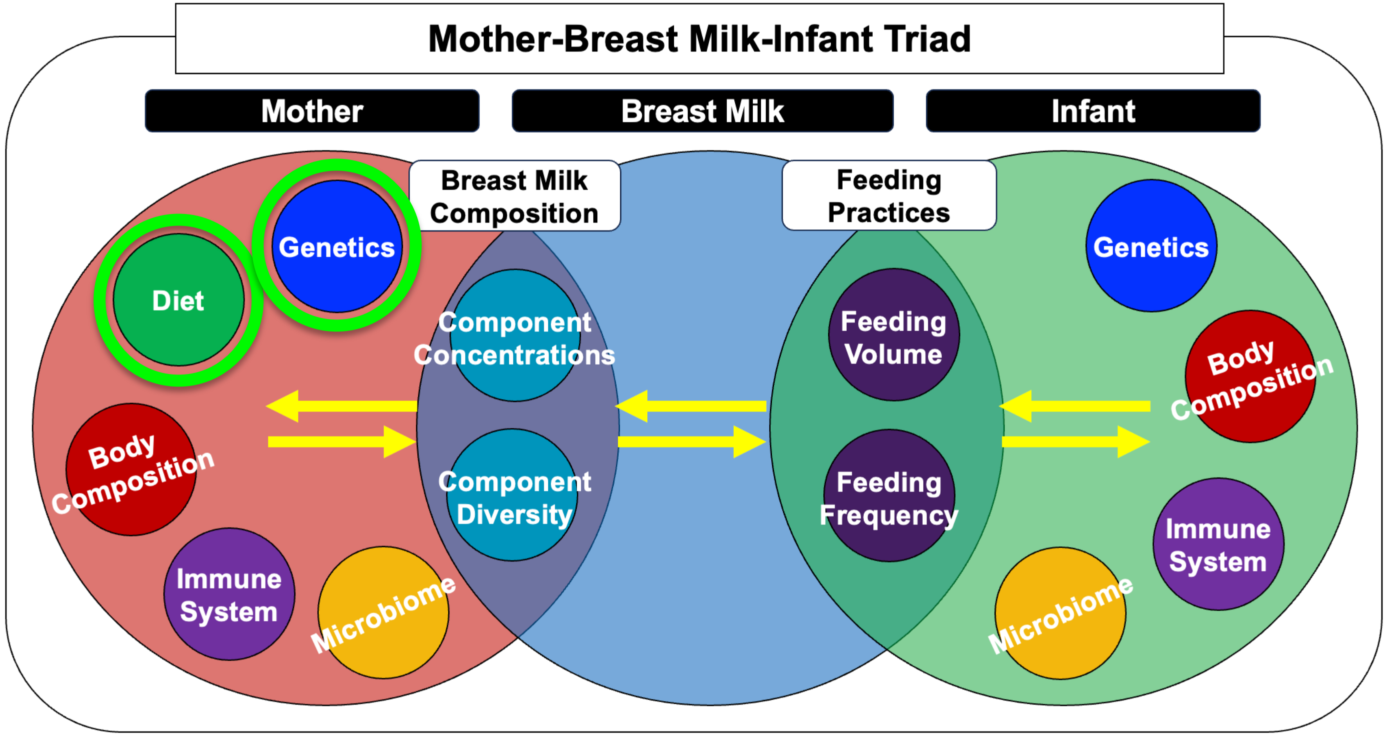
May be attributed in part to biological and environmental influences of human milk composition

Knowledge gap regarding specific human milk components that hold promise for optimizing brain structure/function

Pereyra-Elías R, Quigley MA, Carson C (2022) To what extent does confounding explain the association between breastfeeding duration and cognitive development up to age 14? Findings from the UK Millennium Cohort Study. PLoS ONE 17(5): e0267326;
Jain A, Concato J, Leventhal JM. How good is the evidence linking breastfeeding and intelligence? Pediatrics. 2002 Jun;109(6):1044-53.

WHAT FACTORS SHAPE HUMAN MILK COMPOSITION?

Maternal physiology, breast milk composition, and infant physiology are components of a co-adapting system, and variations in each influence the trajectory of maternal and infant health



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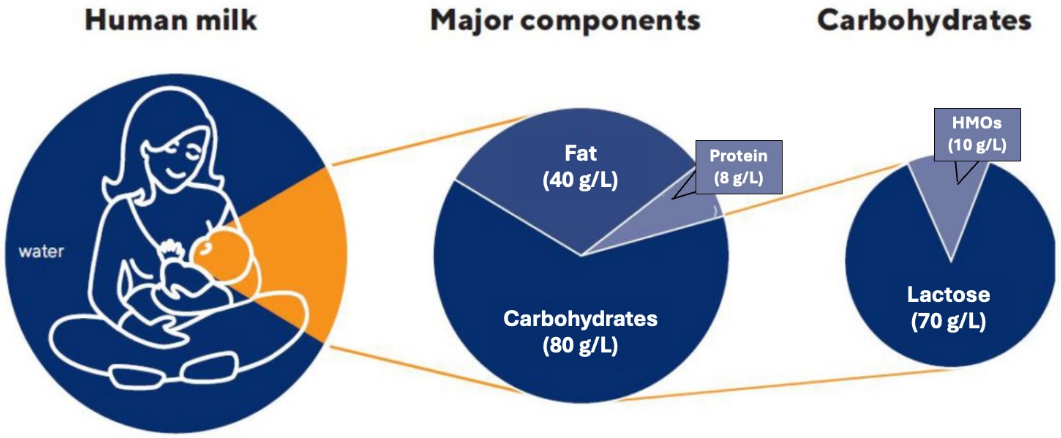
CARBOHYDRATES ARE MOST ABUNDANT COMPONENT OF HUMAN MILK

Major carbohydrate in human milk is lactose, a disaccharide comprised of glucose and galactose

Glucose is main source of energy for early brain development

However, human milk carbohydrates extend beyond lactose

Fructose: structural isomer of glucose, derived from maternal intake of fruits and added sugar and detectable in human milk



Human milk oligosaccharides (HMOs): complex carbohydrates with >200 distinct structures that are naturally occurring in human milk

FRUCTOSE/HFCS TRANSMITTED FROM MOTHER TO NURSING INFANT

Fructose is wide-spread in Western-style diet

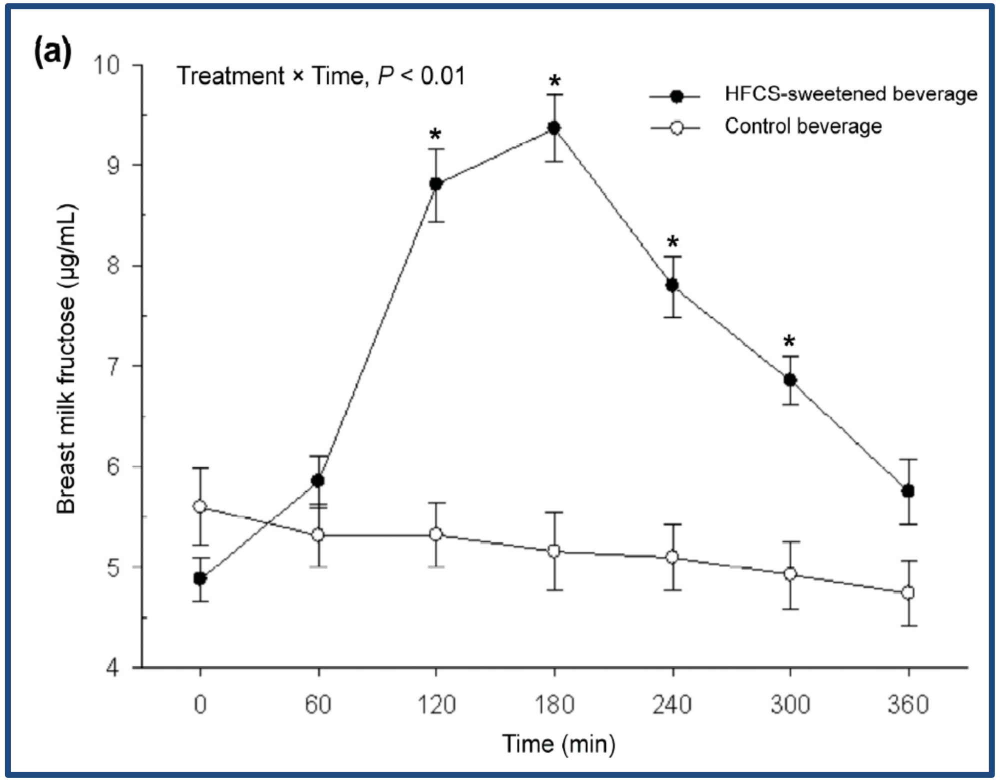
Occurs as high-fructose corn syrup (HFCS), leading source of added sugar in soft drinks

Randomized crossover trial to determine effects of HFCS beverage on human milk carbohydrates (**Fig.**)

Early HFCS exposure induces neuroinflammation in rat pups and impairs learning and memory

Inadvertent transmission from maternal diet to milk may have consequences for nursing infants

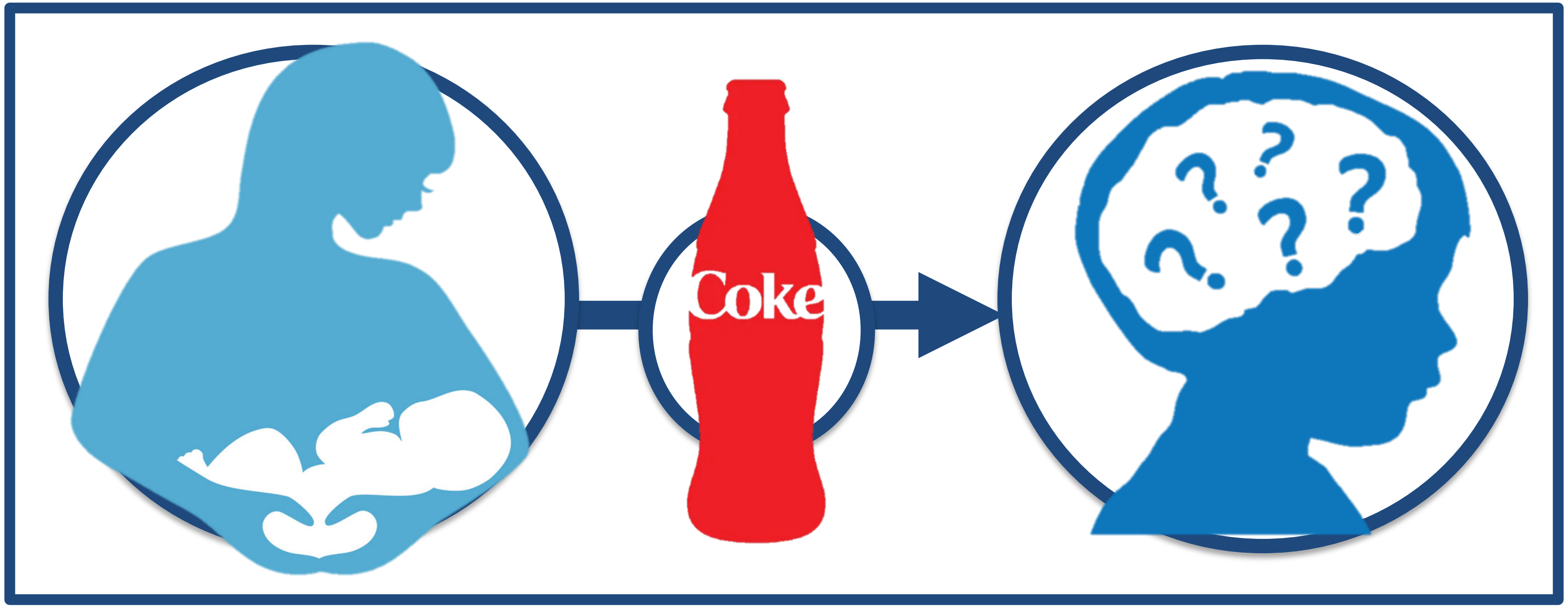
Fig. HFCS Beverage Increased Human Milk Fructose



Berger PK, Fields DA, Demerath EW, Fujiwara H, Goran MI. High-Fructose Corn-Syrup-Sweetened Beverage Intake Increases 5-Hour Breast Milk Fructose Concentrations in Lactating Women. Nutrients. 2018 May 24;10(6):669.

STUDY OBJECTIVE

Determine association of maternal fructose intake during lactation with cognitive development scores in human milk-fed infants, and whether relationship attributed to SSB+J intake



Berger PK, et al. Associations of maternal fructose and sugar-sweetened beverage and juice intake during lactation with infant neurodevelopmental outcomes at 24 months. Am J Clin Nutr. 2020 Dec 10;112(6):1516-1522.

STUDY DESIGN

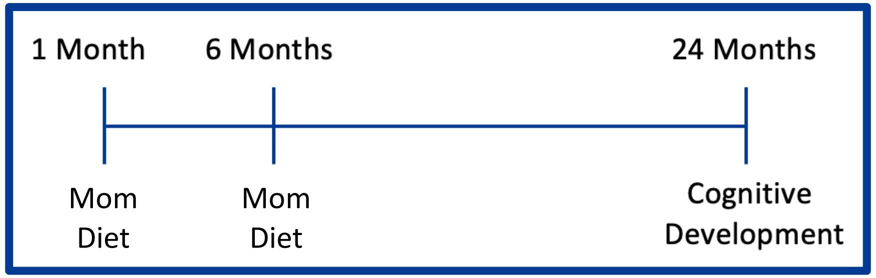
Participants: mothers and human milk-fed full-term infants living in Los Angeles, CA (N=88)

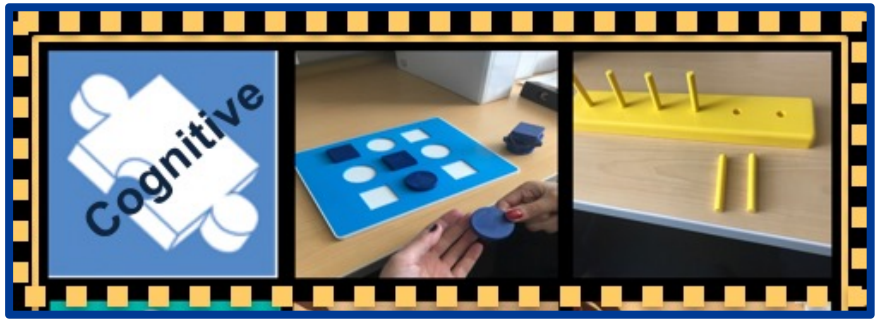
Exposure variables collected at 1 and 6 months of age:

- 24-hour dietary recall
- Maternal intake of fructose, sugar-sweetened beverages/juices, and whole fruits

Outcome variables collected at 24 months of age:

- Bayley Scales of Infant and Child Development
- **Cognitive Scale:** sensorimotor integration, concept formation, attention, habituation, memory





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STUDY RESULTS

TABLE 2 Associations of maternal fructose consumption at 1 postnatal month with infant cognitive development scores at 24 postnatal months[1]

	Model I			Model II			Model III		
	$r^2 = 0.10$			$r^2 = 0.24$			$r^2 = 0.30$		
	B	95% CI	*P*	B	95% CI	*P*	B	95% CI	*P*
Fructose per day at 1 mo	– 0.06	–0.10, –0.02	<0.01	– 0.08	–0.13, –0.03	<0.01	– 0.05	–0.10, 0.00	0.07
SSBs + J per day at 1 mo	—	—		—	—		– 0.29	–0.52, –0.05	0.02
Kilocalories per day at 1 mo	—	—		0.00	0.00, 0.00	0.69	0.00	0.00, 0.00	0.56
Age at delivery	—	—		– 0.01	–0.09, 0.07	0.82	– 0.02	–0.10, 0.05	0.55
Prepregnancy BMI	—	—		– 0.13	–0.21, –0.04	<0.01	– 0.13	–0.21, –0.05	<0.01
Education level	—	—		0.32	–0.04, 0.68	0.08	0.29	–0.06, 0.64	0.11
Infant sex	—	—		– 0.27	–1.25, 0.72	0.59	– 0.36	–1.31, 0.59	0.45
Infant age	—	—		– 0.02	–0.07, 0.03	0.41	– 0.01	–0.06, 0.03	0.56
Infant birthweight	—	—		– 0.22	–1.40, 0.96	0.71	– 0.27	–1.42, 0.88	0.65

[1]Linear regression analyses were conducted to obtain unstandardized (B) coefficients, 95% CIs, and *P* values. Model I includes only maternal fructose consumption at 1 postnatal month as an exposure variable; model II includes maternal age, prepregnancy BMI, education level, kilocalories, infant age, sex, and birthweight as covariates; model III includes maternal SSBs + J at 1 postnatal month as an additional exposure variable ($n = 88$). SSBs + J, sugar-sweetened beverages and juice.

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SSBs + J per day at 1 mo	—	—		—	—		−0.29	−0.52, −0.05	0.02
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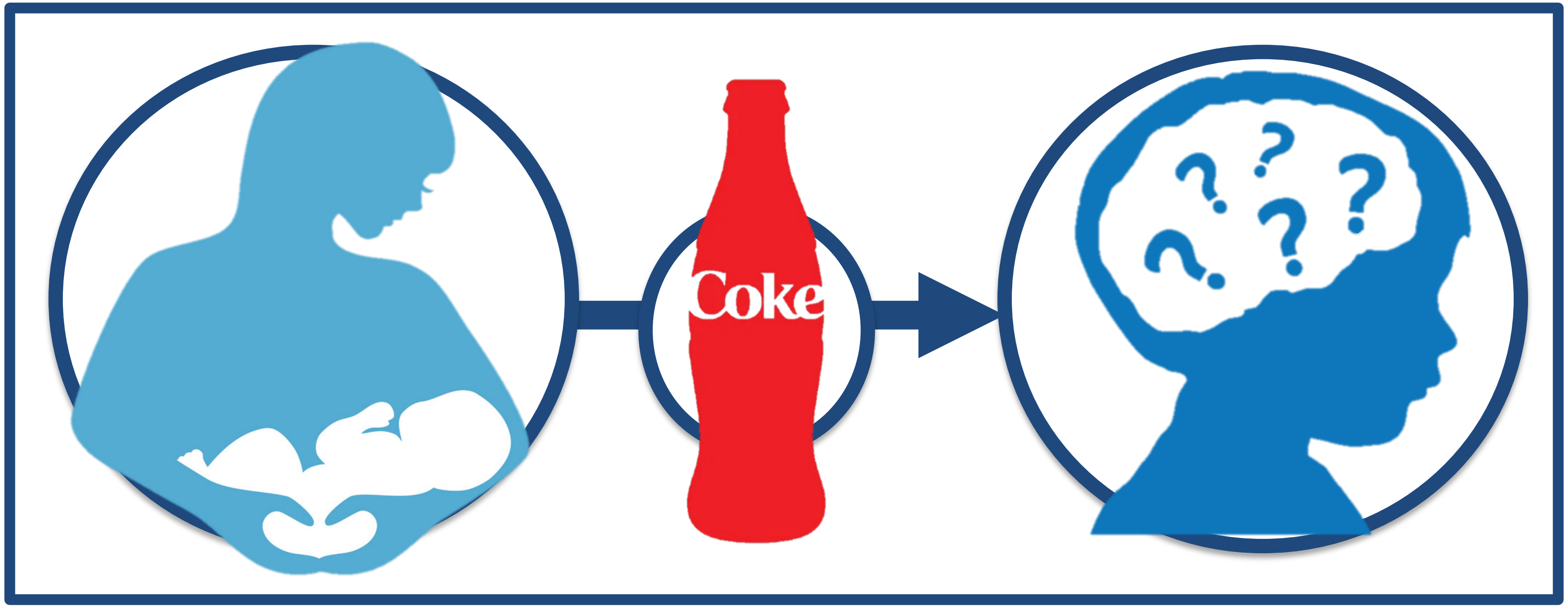
STUDY SUMMARY

Greater intake of fructose in lactating mothers was associated with poorer cognitive development at 24 months in their infants, which may be attributed to greater intake of sugar-sweetened beverages



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FRUCTOSE MAY ALSO BE TRANSMITTED FROM MOTHER TO INFANT IN UTERO

Alternate hypothesis: maternal added sugar intake in lactation reflects enduring patterns from pregnancy

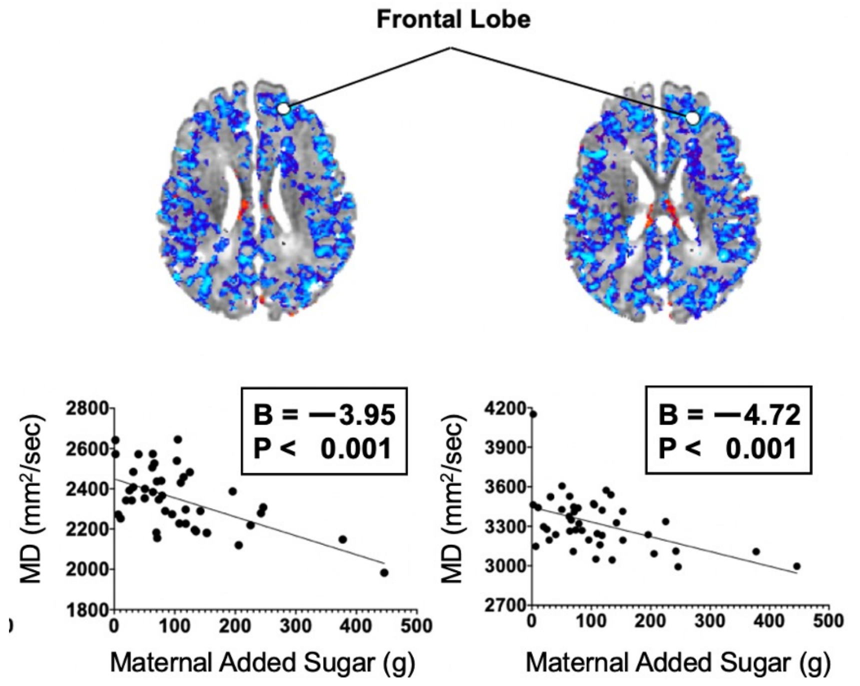
Prospective observational study examining prenatal added sugar intake and newborn brain MRI outcomes

Added sugar intake during second trimester inversely associated with MD values in cortical gray matter (**fig.**)

May reduce dendritic arborization and synaptogenesis, microstructural basis for learning and memory

Results are in line with prior findings– maternal added sugar intake may influence infant neurodevelopment

Fig. Prenatal Added Sugar and MD in Neonatal Brain



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WHAT ARE HUMAN MILK OLIGOSACCHARIDES (HMOS)?

Unconjugated glycans (i.e., **complex carbohydrates**) with >200 distinct structures

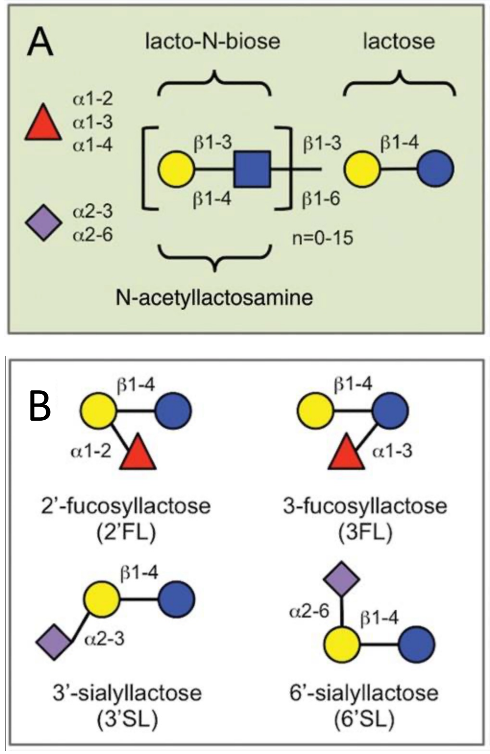
The third most abundant component of human milk

HMO biosynthesis follows a basic structural blueprint

- All contain lactose, which can be elongated with lacto-N-biose or N-acetyllactosamine (**Figure A**)
- May also be fucosylated or sialylated (**Figure B**) to create various HMO subgroups

Slight structural differences may dictate diverse physiological functions, which may be especially important for the brain

Fig. HMO Blueprint.



Bode L. Human milk oligosaccharides: every baby needs a sugar mama. Glycobiology. 2012;22(9):1147-1162.

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WHAT MATERNAL CHARACTERISTICS MAY INFLUENCE HMO COMPOSITION?

Genetics

HMO composition mirrors blood group characteristics

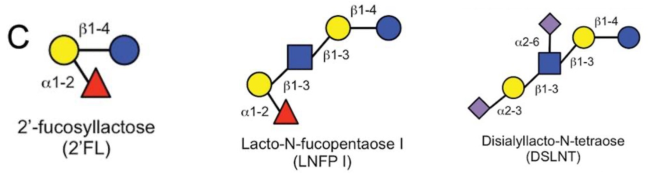
Women with active secretor locus encoding for FUT2 enzyme classified as **Secretors**

- Human milk abundant in 2′-fucosyllactose (2′FL) and LNFP I

Those who lack a functional FUT2 enzyme are **Non-Secretors**

- Human milk does not contain α1-2-fucosylated HMOs

In addition to FUT2-dependent HMOs, most other HMOs also differ between Secretors and Non-Secretors



	Total (n=157)	Non-Secretors (n=22)	Secretors (n=135)	p^b
2'FL	2716 ± 1579	46.6 ± 69.9	3155 ± 1238	<0.01
3FL	201.7 ± 172	244.5 ± 386	194.6 ± 103	0.21
3'SL	355.6 ± 357	295.1 ± 246	365.5 ± 372	0.39
6'SL	625.1 ± 209	729.4 ± 249	607.9 ± 198	0.01
DFLac	279.7 ± 217	28.2 ± 33.8	321.0 ± 206	<0.01
LNT	806.4 ± 516	1068 ± 808	763.5 ± 440	0.01
LNnT	440.8 ± 253	388.5 ± 378	449.4 ± 227	0.30
LNFPI	1498 ± 957	392.8 ± 636	1680 ± 876	<0.01
LNFPII	873.0 ± 565	1669 ± 874	742.2 ± 359	<0.01
LNFPIII	60.1 ± 36.1	86.2 ± 38.9	55.8 ± 33.9	<0.01
LSTb	89.1 ± 57.0	126.9 ± 58.7	82.8 ± 54.5	<0.01
LSTc	318.2 ± 140	263.6 ± 107	327.2 ± 144	0.05
DFLNT	1481 ± 754	1072 ± 704	1548 ± 743	0.01
DSLNT	477.1 ± 228	454.9 ± 240	480.7 ± 226	0.62
LNH	90.1 ± 57.1	97.3 ± 69.4	89.0 ± 55.1	0.53
FLNH	147.8 ± 92.8	162.4 ± 115	145.5 ± 89.0	0.43
DFLNH	229.2 ± 196	100.9 ± 129	250.3 ± 197	<0.01
FDSLNH	315.1 ± 387	915.7 ± 671	216.4 ± 185	<0.01
DSLNH	436.5 ± 185	566.6 ± 213	415.2 ± 172	<0.01

1) Bode L. Human milk oligosaccharides: every baby needs a sugar mama. Glycobiology. 2012;22(9):1147-1162; 2) Azad MB. Human Milk Oligosaccharide Concentrations Are Associated with Multiple Fixed and Modifiable Maternal Characteristics, Environmental Factors, and Feeding Practices. J Nutr. 2018 Nov 1;148(11):1733-1742; 3) Berger PK. Human Milk Oligosaccharides and Hispanic Infant Weight Gain in the First 6 Months. Obesity (Silver Spring). 2020 Aug;28(8):1519-1525.

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WHICH HMO STRUCTURES ARE RELATED TO BRAIN DEVELOPMENT? HOW?

HMOs ingested during human milk feeding reach distal small intestine and colon in an intact form

Bode L. *Glycobiology*. 2012 Sep;22(9):1147-62; Wall R, et al. *Adv Exp Med Biol*. 2014;817:221-239; Yu ZT, et al. *Glycobiology*. 2013;23(11):1281-1292.

WHICH HMO STRUCTURES ARE RELATED TO BRAIN DEVELOPMENT? HOW?

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- Source of **prebiotics** selectively fed on by beneficial bacteria within the gut microbiome

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Neuroactive metabolites may affect enteric nervous system or absorbed by colonocytes and enter vagus nerve

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1. Regulation of brain-derived neurotrophic factor– supports neuronal differentiation and circuit formation

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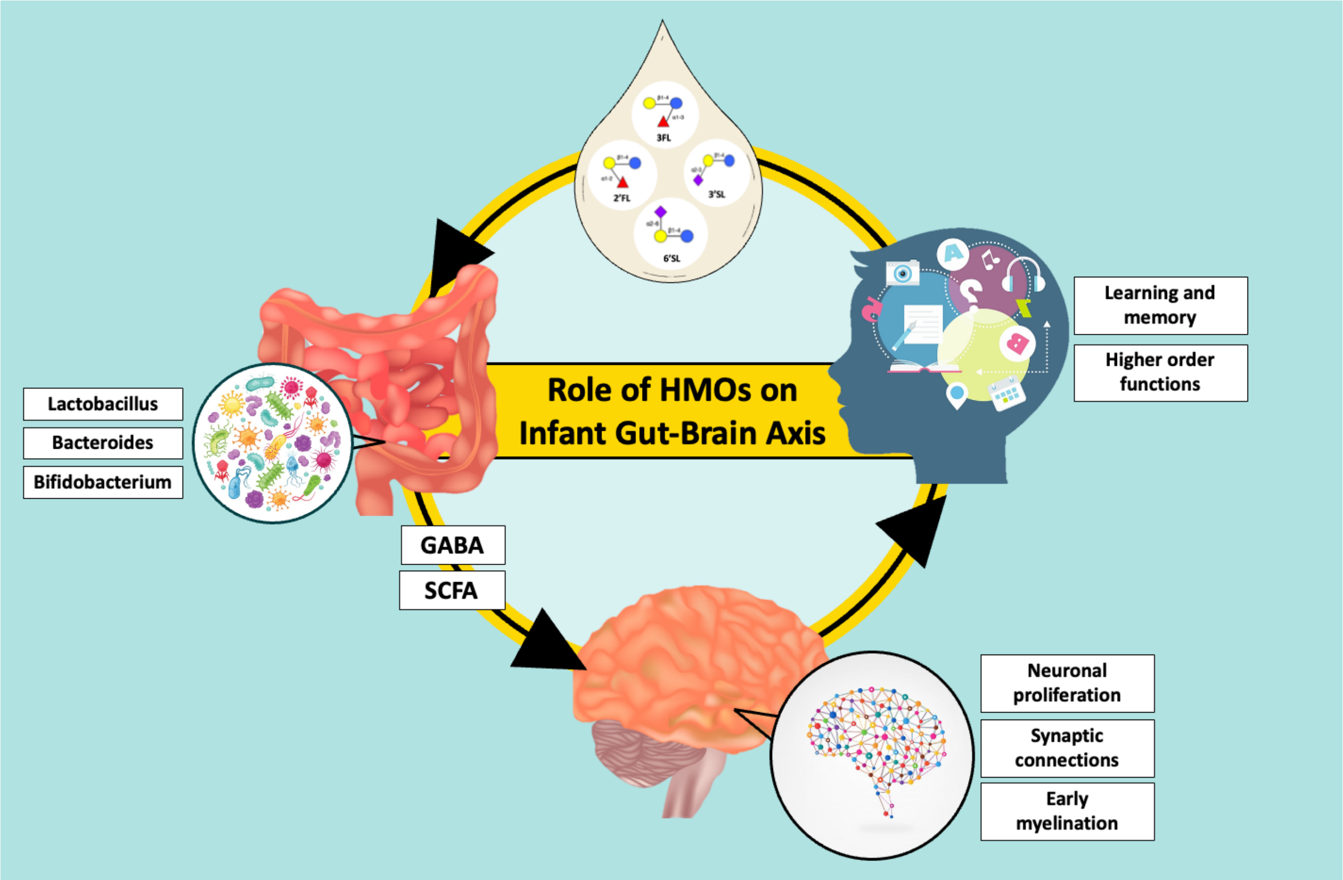
Neuroactive metabolites may affect enteric nervous system or absorbed by colonocytes and enter vagus nerve

1. Regulation of brain-derived neurotrophic factor– supports neuronal differentiation and circuit formation
2. Induction of T-reg cells and interleukins– enter systemic circulation and may reduce neuroinflammation

Bode L. *Glycobiology*. 2012 Sep;22(9):1147-62; Wall R, et al. *Adv Exp Med Biol*. 2014;817:221-239; Yu ZT, et al. *Glycobiology*. 2013;23(11):1281-1292.

POTENTIAL MECHANISM THROUGH WHICH HMOS AFFECT INFANT BRAIN



HMOS AND INFANT NEURODEVELOPMENT: A NARRATIVE REVIEW

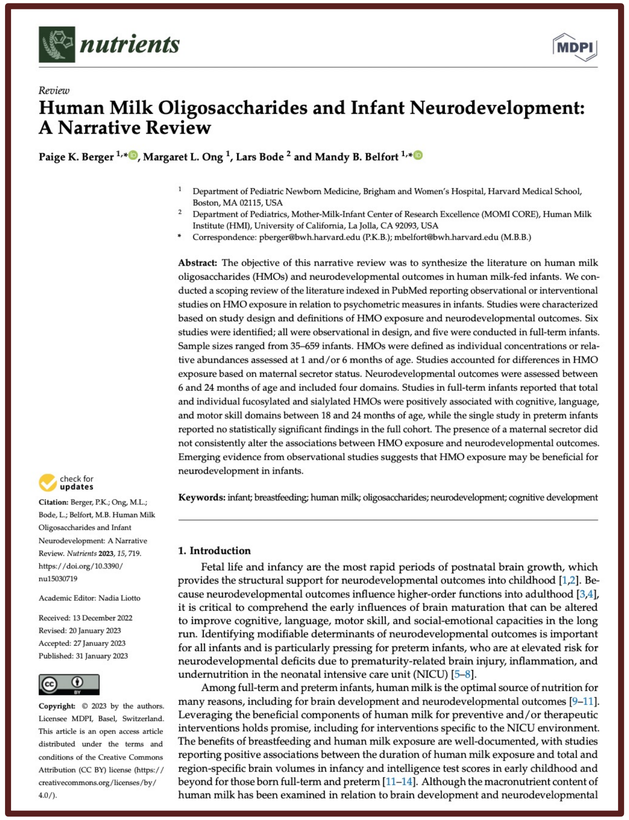
Scoping review on associations of HMOs with neurodevelopmental outcomes in human milk-fed infants

6 studies identified, all observational in design, 5 in full-term infants

Exposure variables defined as individual concentrations of HMOs or relative abundances of HMOs at 1 and/or 6 months

Neurodevelopmental outcomes assessed between 6 and 24 months

Total and individual fucosylated and sialylated HMOs associated with cognitive, language, motor skill domains between 18-24 months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Review

Human Milk Oligosaccharides and Infant Neurodevelopment: A Narrative Review

Paige K. Berger [1,*], Margaret L. Ong [1], Lars Bode [2] and Mandy B. Belfort [1,*]

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2 Department of Pediatrics, Mother-Milk-Infant Center of Research Excellence (MOMI CORE), Human Milk Institute (HMI), University of California, La Jolla, CA 92093, USA
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Abstract: The objective of this narrative review was to synthesize the literature on human milk oligosaccharides (HMOs) and neurodevelopmental outcomes in human milk-fed infants. We conducted a scoping review of the literature indexed in PubMed reporting observational or interventional studies on HMO exposure in relation to psychometric measures in infants. Studies were characterized based on study design and definitions of HMO exposure and neurodevelopmental outcomes. Six studies were identified; all were observational in design, and five were conducted in full-term infants. Sample sizes ranged from 35–659 infants. HMOs were defined as individual concentrations or relative abundances assessed at 1 and/or 6 months of age. Studies accounted for differences in HMO exposure based on maternal secretor status. Neurodevelopmental outcomes were assessed between 6 and 24 months of age and included four domains. Studies in full-term infants reported that total and individual fucosylated and sialylated HMOs were positively associated with cognitive, language, and motor skill domains between 18 and 24 months of age, while the single study in preterm infants reported no statistically significant findings in the full cohort. The presence of a maternal secretor did not consistently alter the associations between HMO exposure and neurodevelopmental outcomes. Emerging evidence from observational studies suggests that HMO exposure may be beneficial for neurodevelopment in infants.

Keywords: infant; breastfeeding; human milk; oligosaccharides; neurodevelopment; cognitive development

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1. Introduction

Fetal life and infancy are the most rapid periods of postnatal brain growth, which provides the structural support for neurodevelopmental outcomes into childhood [1,2]. Because neurodevelopmental outcomes influence higher-order functions into adulthood [3,4], it is critical to comprehend the early influences of brain maturation that can be altered to improve cognitive, language, motor skill, and social-emotional capacities in the long run. Identifying modifiable determinants of neurodevelopmental outcomes is important for all infants and is particularly pressing for preterm infants, who are at elevated risk for neurodevelopmental deficits due to prematurity-related brain injury, inflammation, and undernutrition in the neonatal intensive care unit (NICU) [5–8].

Among full-term and preterm infants, human milk is the optimal source of nutrition for many reasons, including for brain development and neurodevelopmental outcomes [9–11]. Leveraging the beneficial components of human milk for preventive and/or therapeutic interventions holds promise, including for interventions specific to the NICU environment. The benefits of breastfeeding and human milk exposure are well-documented, with studies reporting positive associations between the duration of human milk exposure and total and region-specific brain volumes in infancy and intelligence test scores in early childhood and beyond for those born full-term and preterm [11–14]. Although the macronutrient content of human milk has been examined in relation to brain development and neurodevelopmental

Berger PK, et al. Nutrients. 2023 Jan 31;15(3):719.

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STUDY OBJECTIVE

Determine associations of HMO exposure at 1 month MRI measures of structural brain development at 1 month in milk-fed full-term infants

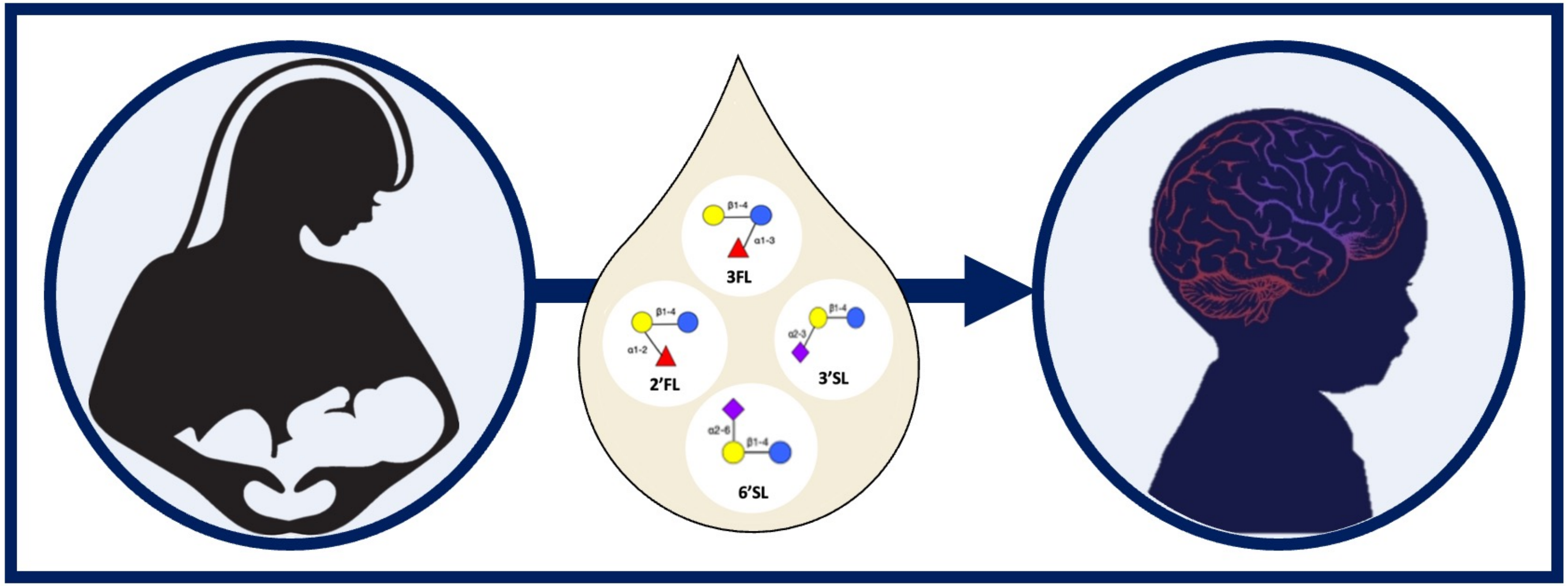

Image created by author and adapted from: 1) Bode L. Human milk oligosaccharides: every baby needs a sugar mama. Glycobiology. 2012 Sep;22(9):1147-62; 2) https://www.123rf.com/free-stock-images/breastfeeding_stock_vectors_clipart_and_illustrations.html?oriSearch=breastfeeding&page=2; 3) https://myimi.uk/5-amazing-facts-about-your-babys-brain/

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STUDY DESIGN

Participants: mothers and their human milk-fed full-term infants living in Los Angeles, CA (N=40)

Exposure variables collected at 1 month of age:

Human milk samples analyzed for 19 most abundant HMOs

Initial focus on concentrations of 2’FL and 3FL (and 3’SL and 6’SL)

Outcome variables also collected at 1 month of age:

Brain images obtained using a 3T MRI scanner

Diffusion measures of brain tissue microstructure– **fractional anisotropy (FA)** and **mean diffusivity (MD)**

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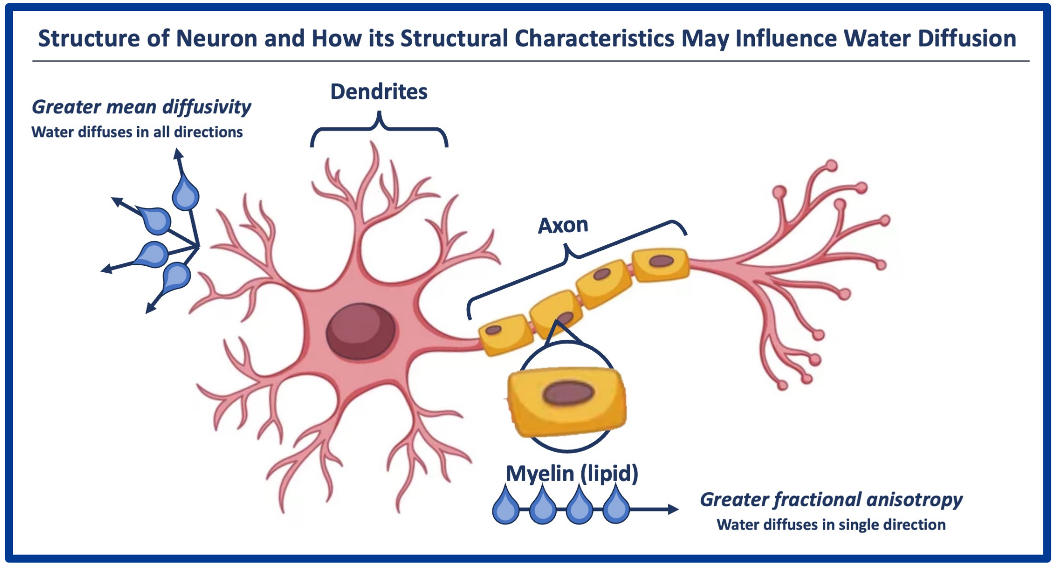
Berger PK, et al. *Nutrients.* 2022 Sep 16;14(18):3820.

OUTCOME MEASURES OF BRAIN TISSUE MICROSTRUCTURE VIA MRI

DTI: measures movement of water modulated by characteristics of brain tissue microstructure

- Indexed by FA and MD values



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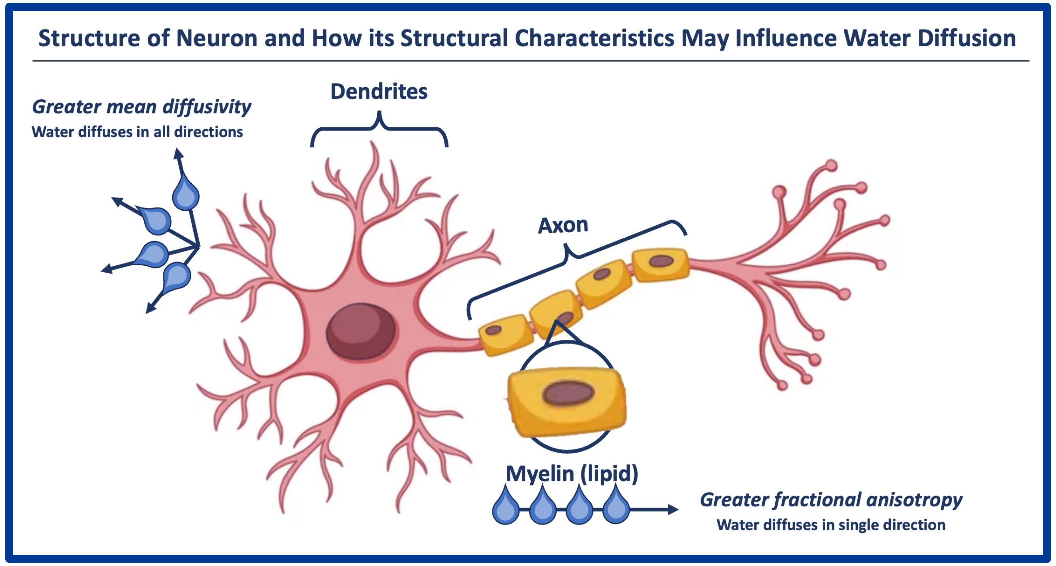
Fractional anisotropy (FA):

Diffusion of water in a single direction

In developing white matter, may reflect greater **myelination**



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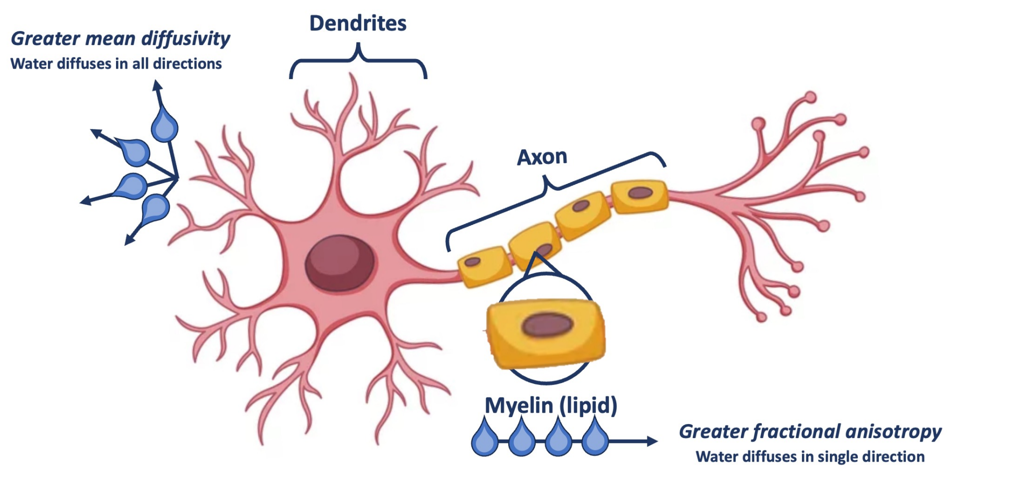
Structure of Neuron and How its Structural Characteristics May Influence Water Diffusion



Mean diffusivity (MD):

- Diffusion of water in all directions without specificity
- In areas of cortical gray matter, may reflect greater **dendritic arborization**

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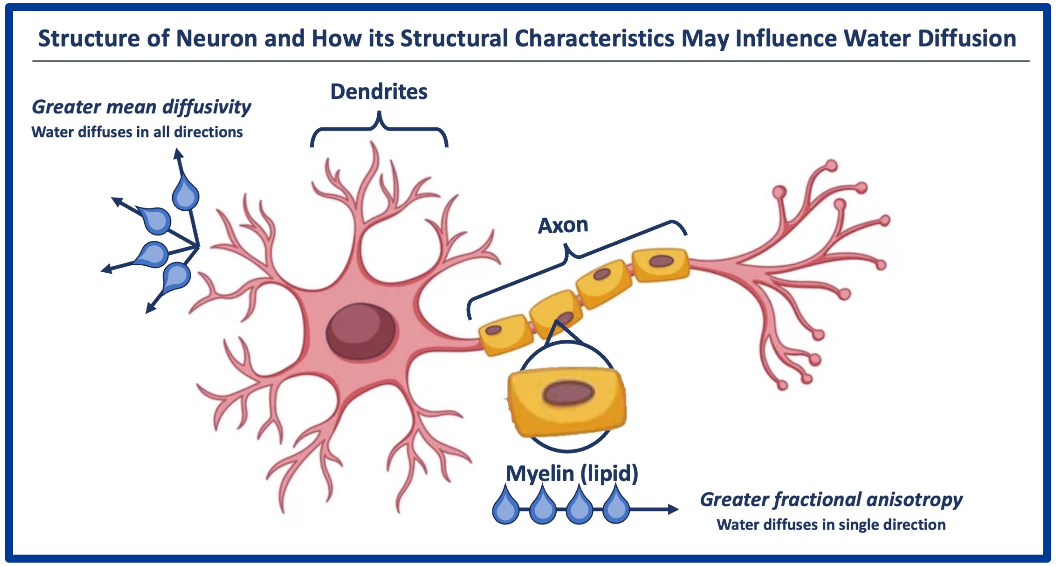

Mean diffusivity (MD):

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Dendritic arborization is structural basis **for learning/memory** & myelination essential for **higher-order functions**

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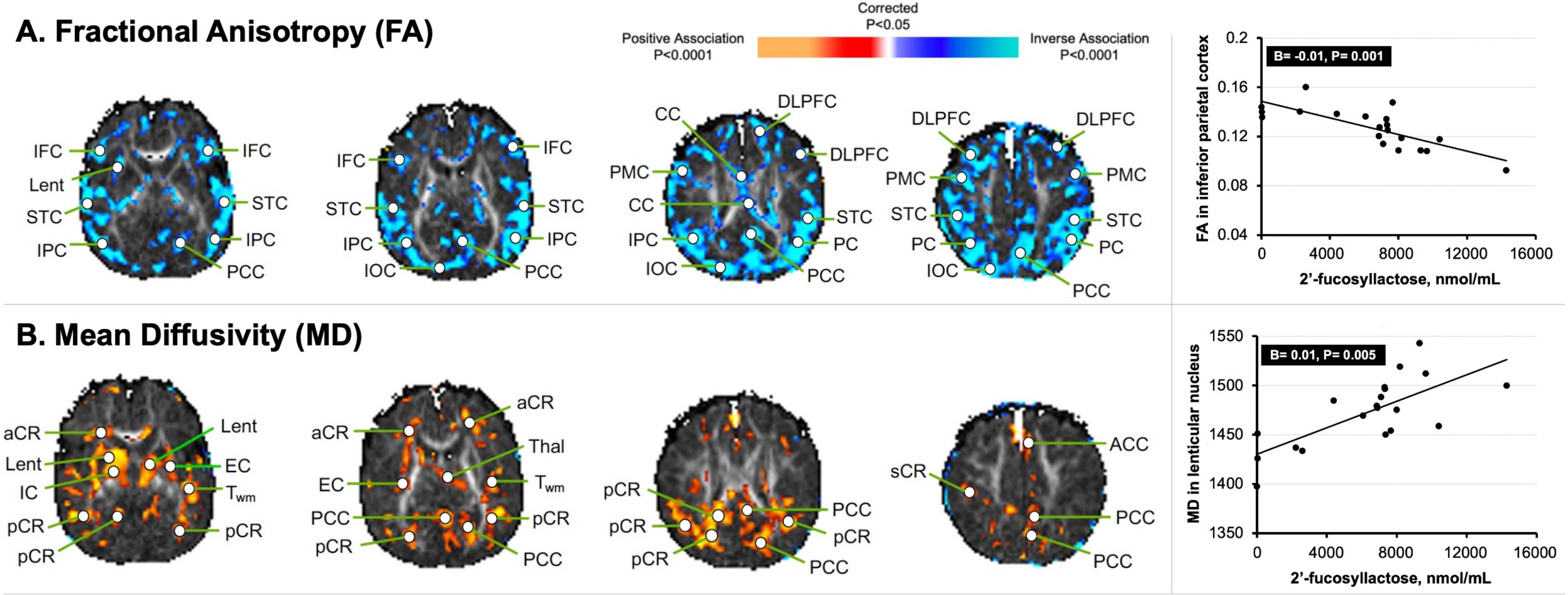
ASSOCIATIONS OF 2’FL CONCENTRATIONS WITH MRI OUTCOMES



Statistical maps of 2’FL exposure at 1-month of age with newborn MRI measures. The statistical significance of the associations of 2’FL exposure with measures of brain tissue microstructure at each point on the surface of the brain is color-coded, with warm colors representing significant positive associations and cool colors representing significant inverse associations. Only P-values that survived FDR correction are plotted.

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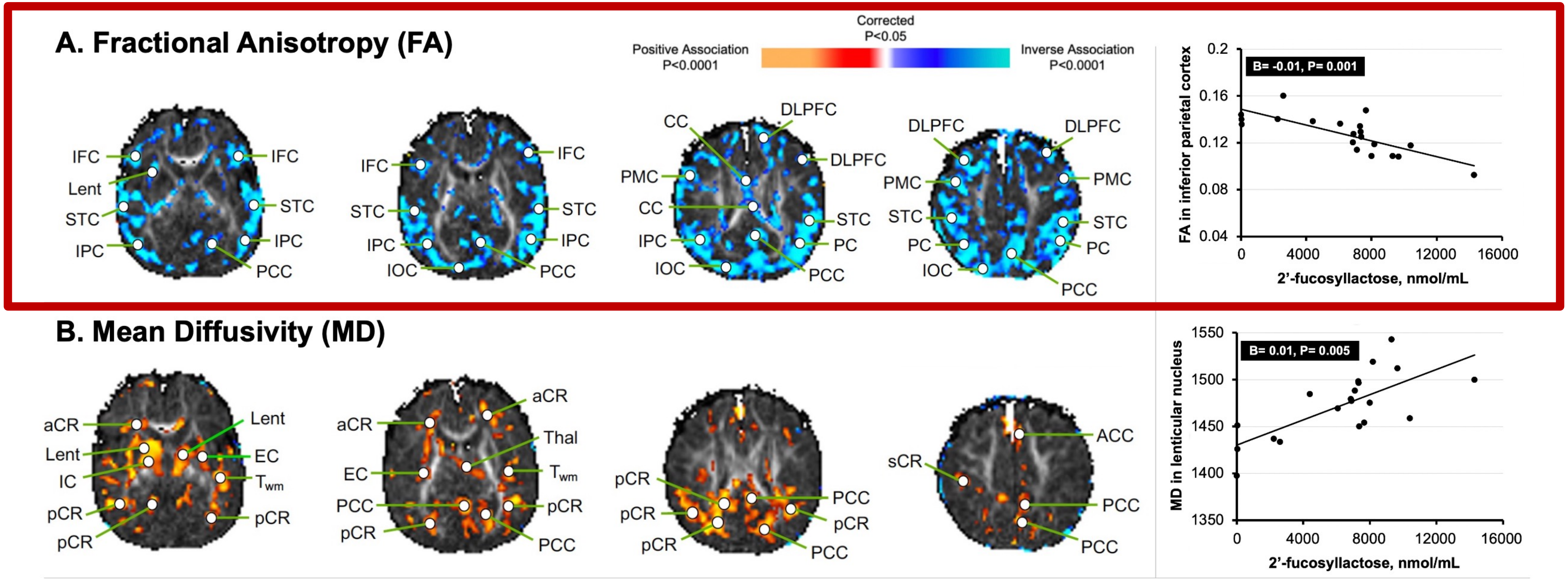

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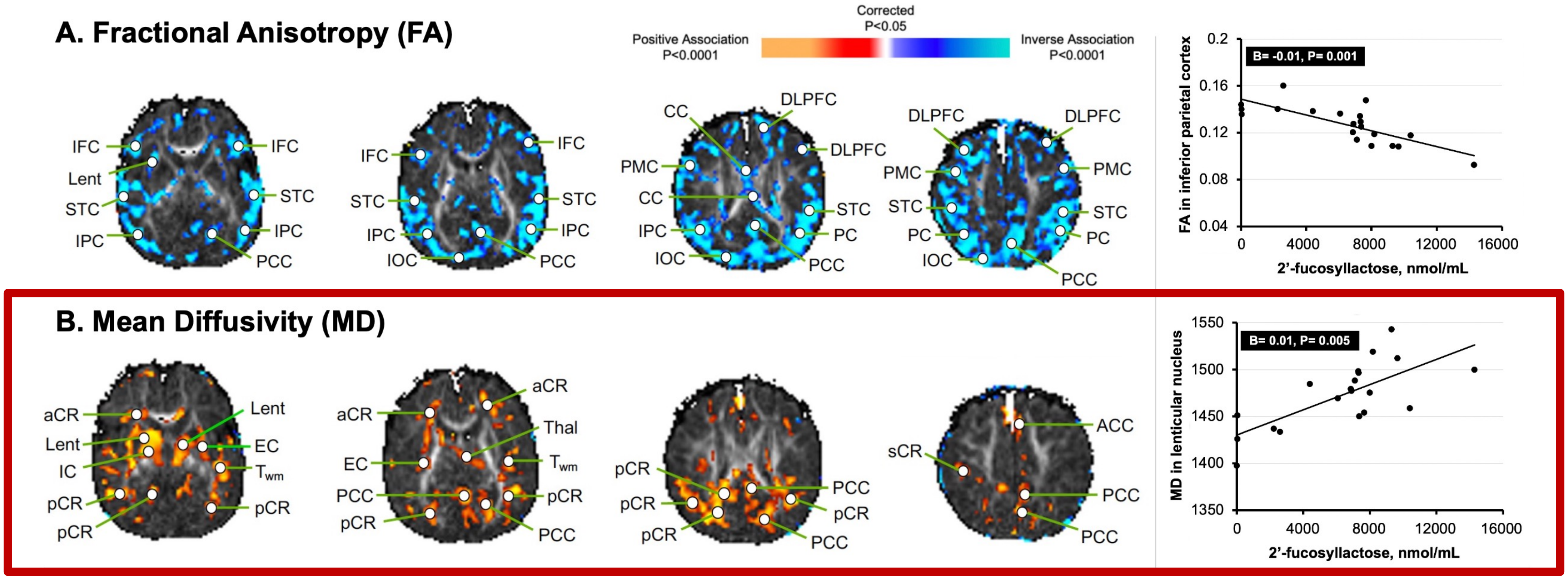

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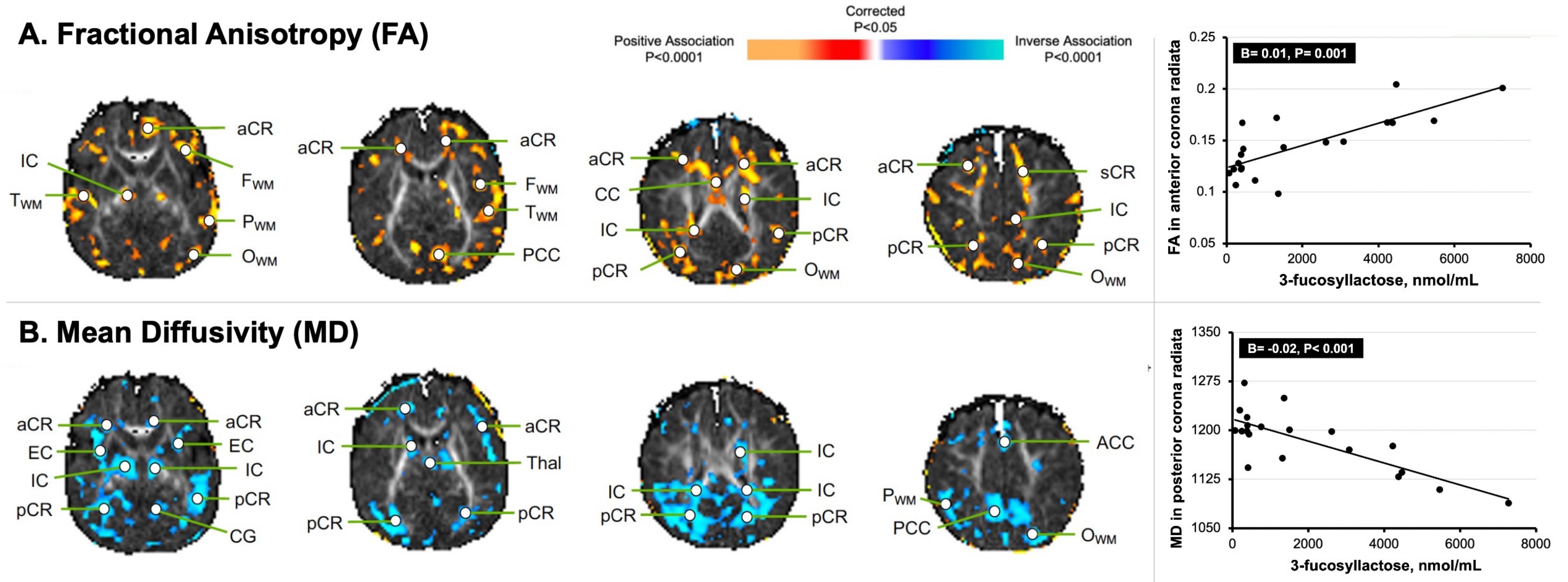
ASSOCIATIONS OF 3FL CONCENTRATIONS WITH MRI OUTCOMES



Statistical maps of 3FL exposure at 1-month of age with newborn MRI measures. The statistical significance of the associations of 3FL exposure with measures of brain tissue microstructure at each point on the surface of the brain is color-coded, with warm colors representing significant positive associations and cool colors representing significant inverse associations. Only P-values that survived FDR correction are plotted.

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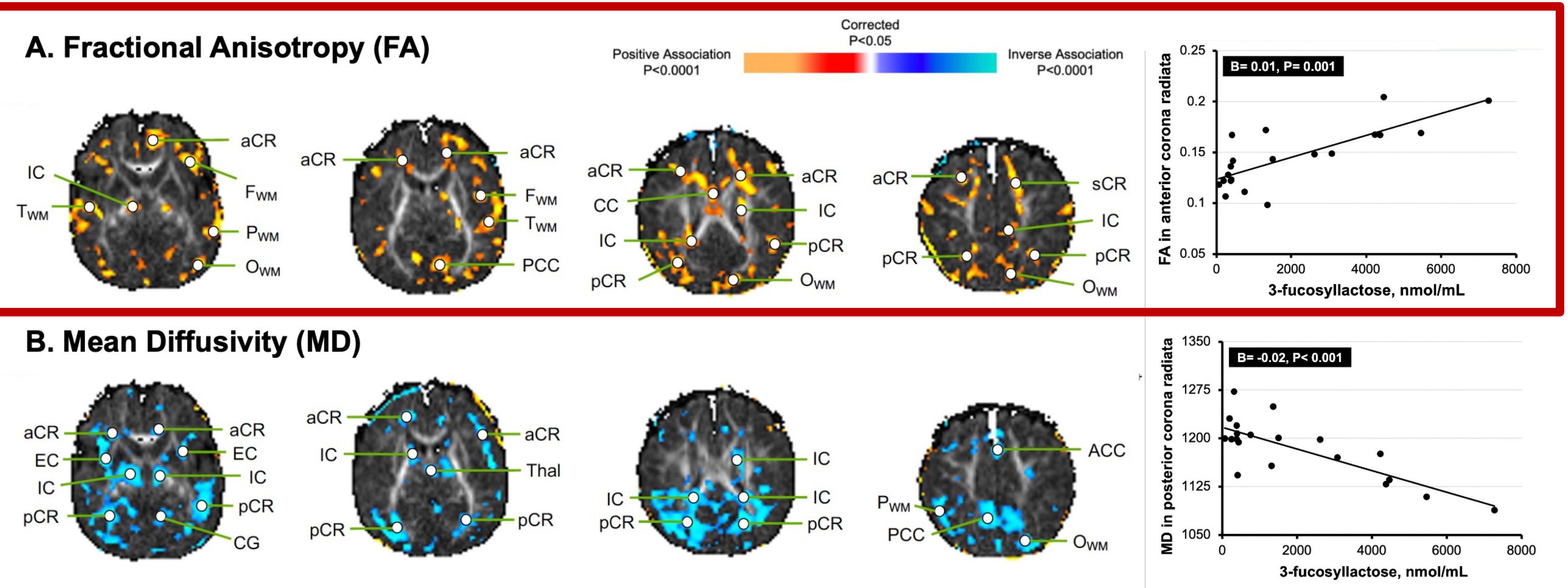
ASSOCIATIONS OF 3FL CONCENTRATIONS WITH MRI OUTCOMES



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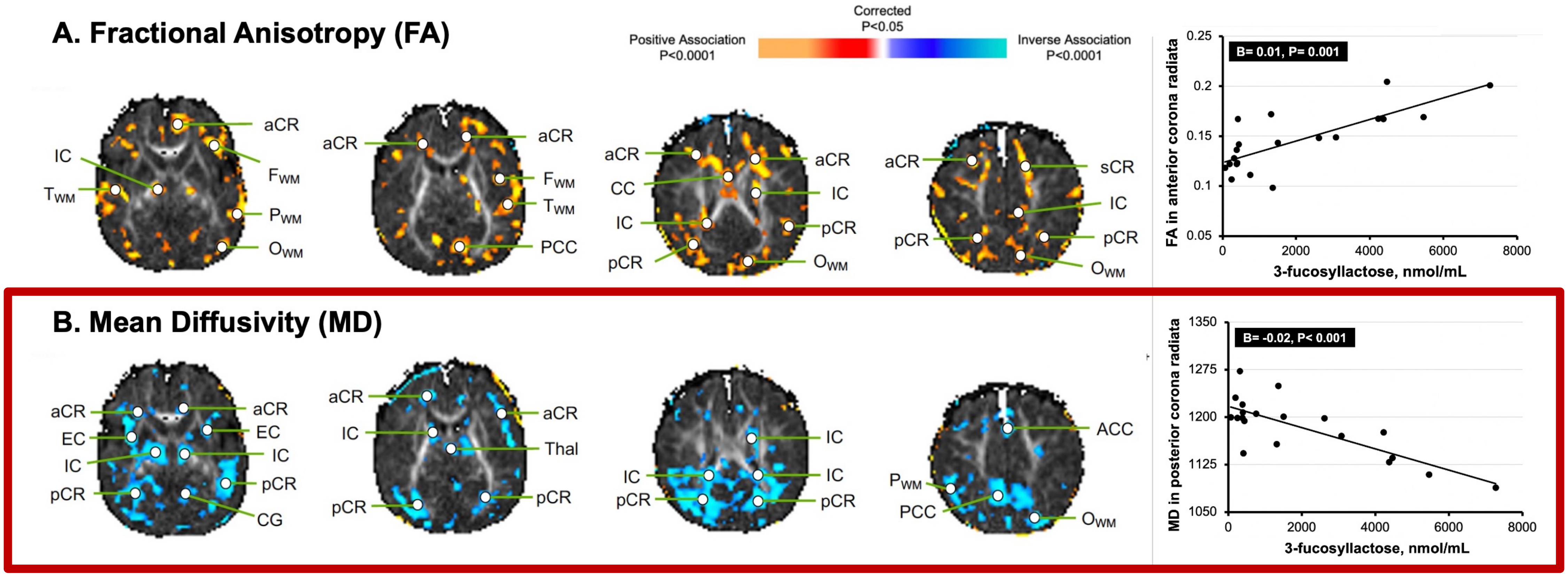
ASSOCIATIONS OF 3FL CONCENTRATIONS WITH MRI OUTCOMES



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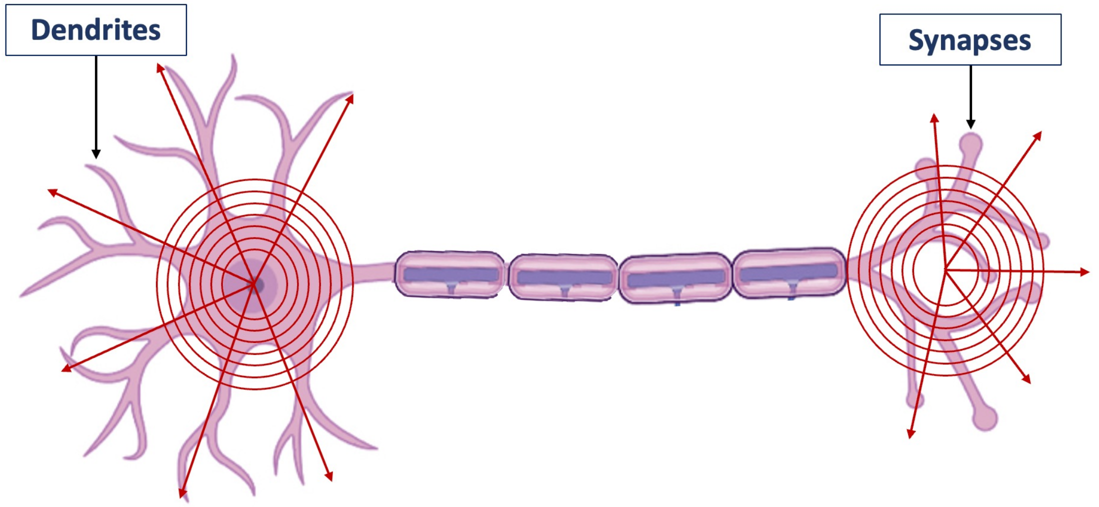
HMOS MAY HAVE DISTINCT YET COMPLEMENTARY INFLUENCES ON INFANT BRAIN

2′FL may enhance dendritic arborization:

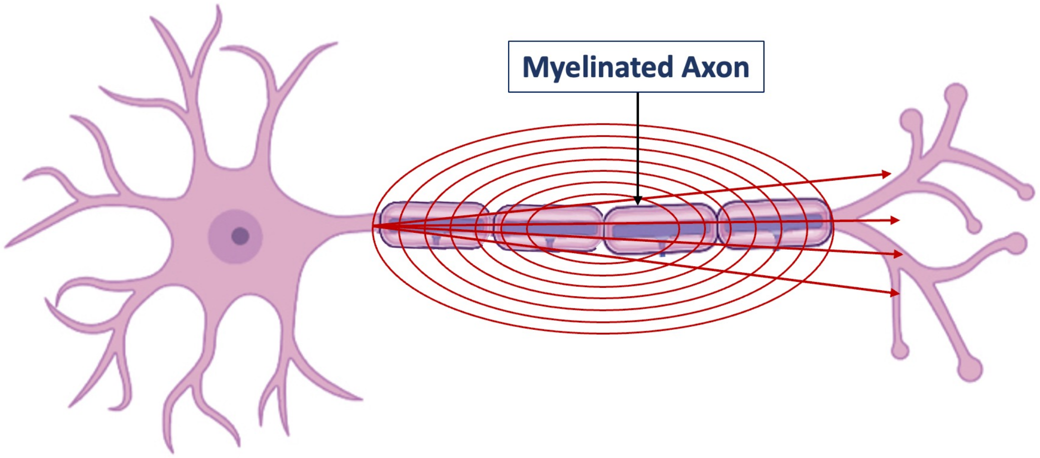
Dendrites and synapses branch in all directions, reflected in lower FA and greater MD in cortex



Lower FA, higher MD in areas of cortical gray matter

3FL may enhance myelination:

Constrains movement of water in one direction, reflected in greater FA and lower MD in white matter



Higher FA, lower MD in areas of developing white matter

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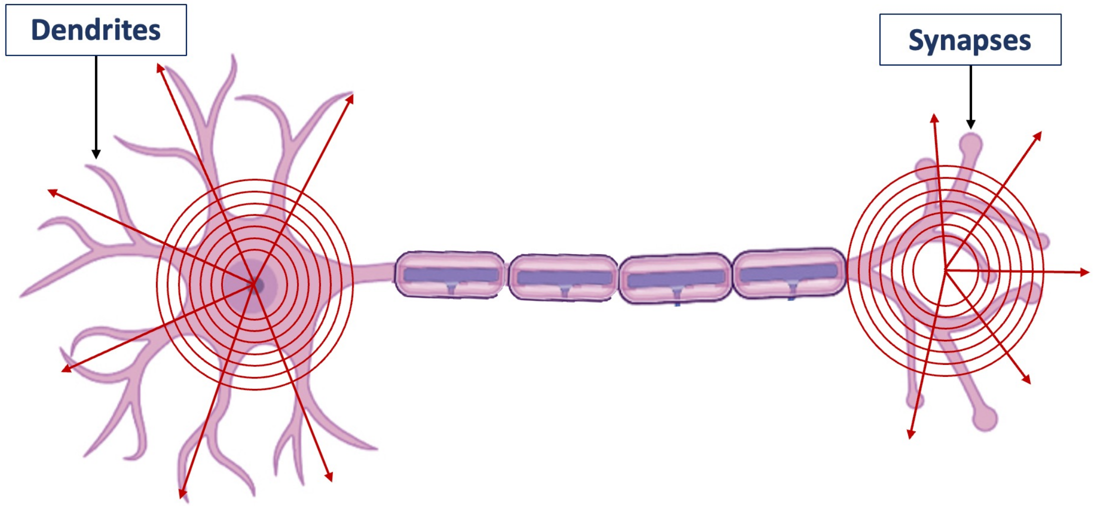

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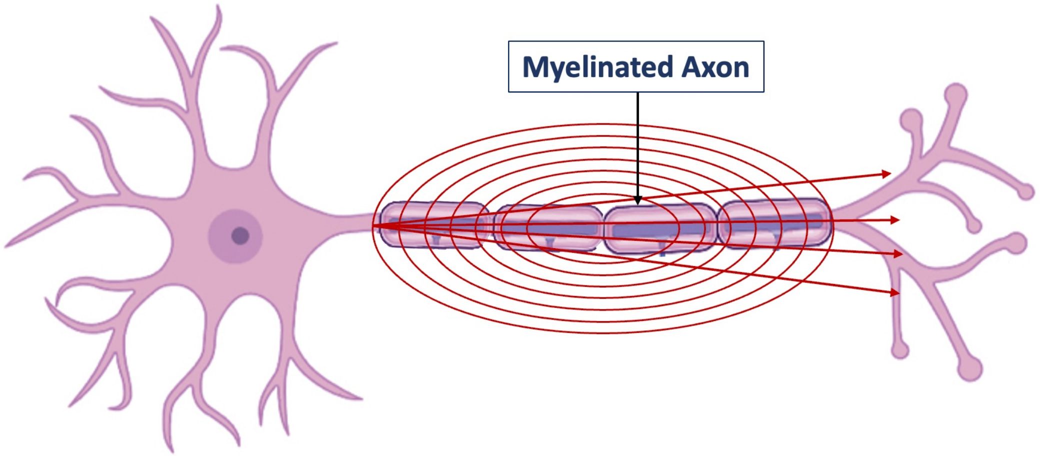

Higher FA, lower MD in areas of developing white matter

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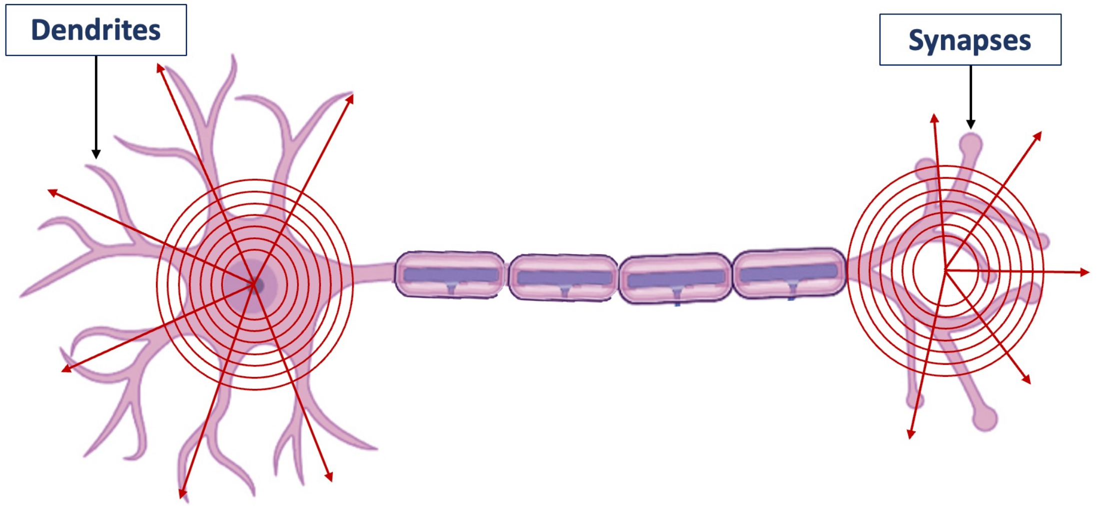

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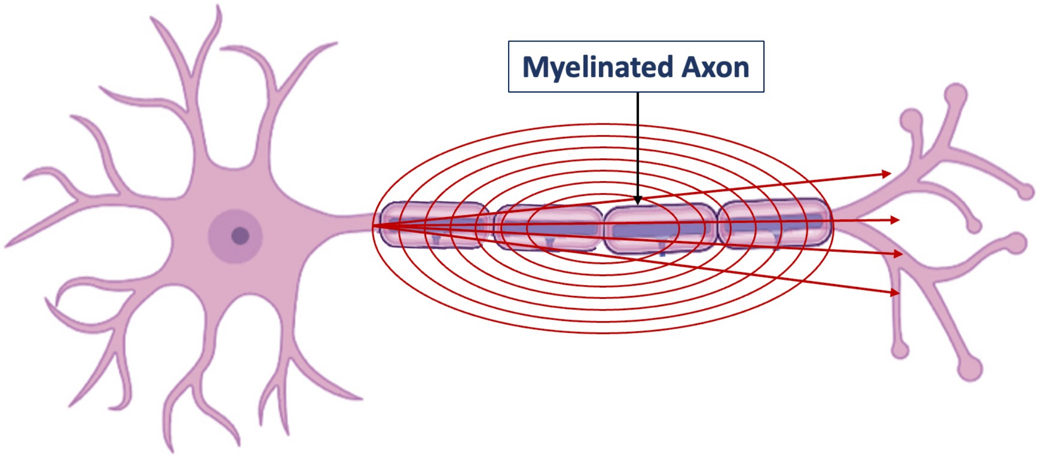

Higher FA, lower MD in areas of developing white matter

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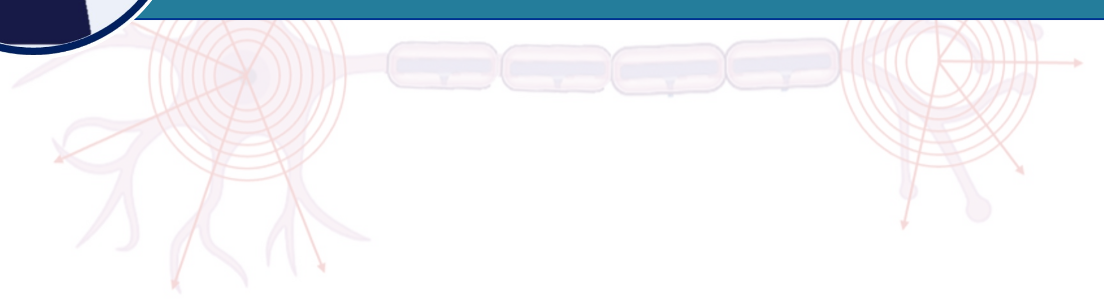
HMOS MAY HAVE DISTINCT YET COMPLEMENTARY INFLUENCES ON INFANT BRAIN

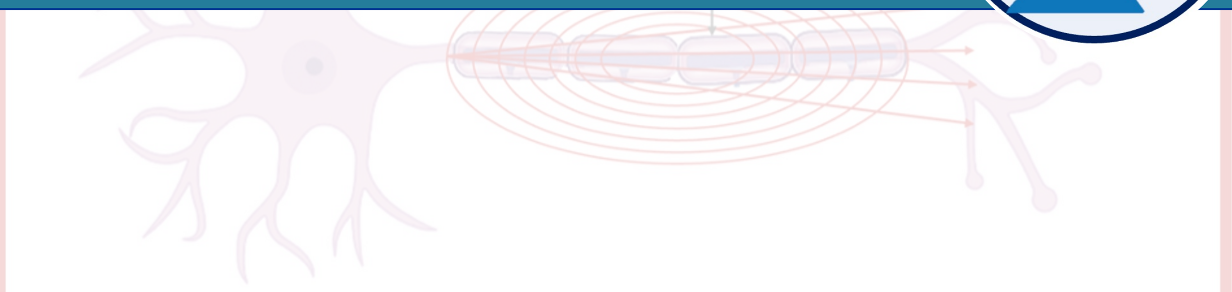
2′FL may enhance dendritic arborization:
Dendrites and synapses branch in all directions, reflected in lower FA and greater MD in cortex

3FL and 3′SL may enhance myelination:
Constrains movement of water in one direction, reflected in greater FA and lower MD in white matter

Dendritic arborization is structural basis for learning/memory & myelination essential for higher-order cognitive functions



Lower FA, higher MD in areas of cortical gray matter



Higher FA, lower MD in areas of developing white matter

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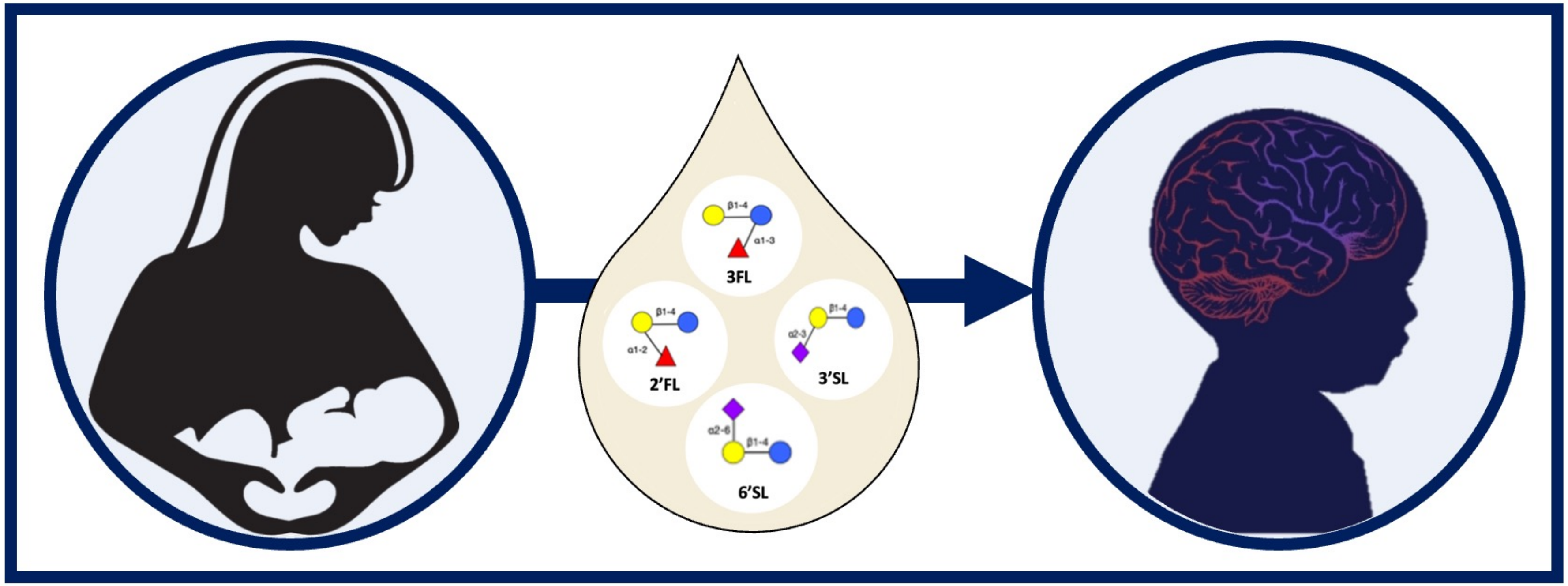
STUDY SUMMARY

Individual HMOs, defined by distinct structural characteristics, differentially associate with MRI indices of brain tissue microstructure in human milk-fed full-term infants



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HMOS MAY BE ESPECIALLY BENEFICIAL FOR PRETERM BRAIN

Despite advancements in neonatal medicine and clinical care, half of very preterm infants (<32 weeks' gestation) have a heightened risk for neurodevelopmental deficits after discharge from NICU

The 2-4-month period of NICU hospitalization coincides with a critical window in which the brain undergoes extensive structural development

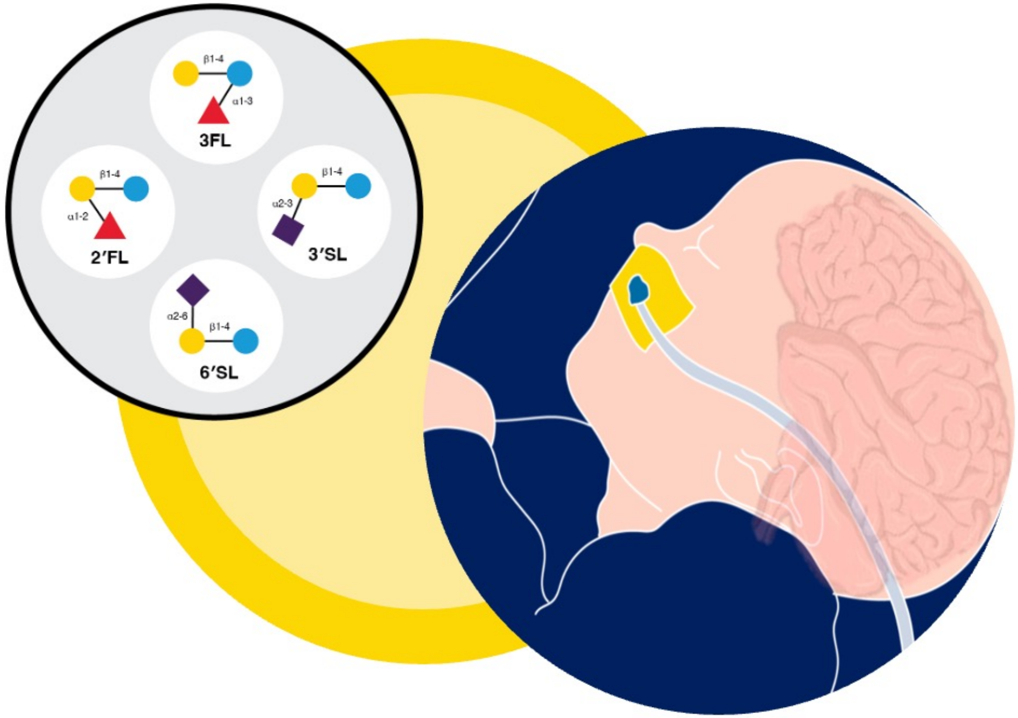
At the same time, very preterm infants exposed to intense clinical environment that may shape structural brain development, including pharmacological treatments, invasive procedures, physical stress, and social isolation

While these exposures may be essential for medical management and overall well-being, NICU diet represents a highly modifiable influence of brain development that may be optimized during this critical period

Human milk diet recommended for virtually all very preterm infants and HMO exposure may be neuroprotective

STUDY OBJECTIVE

Determine associations of HMO exposure during NICU hospitalization with MRI measures of total/regional brain volumes in milk-fed very preterm infants



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STUDY DESIGN

Participants: human milk-fed very preterm infants (<32 weeks of gestation) in Boston, MA (N=62)

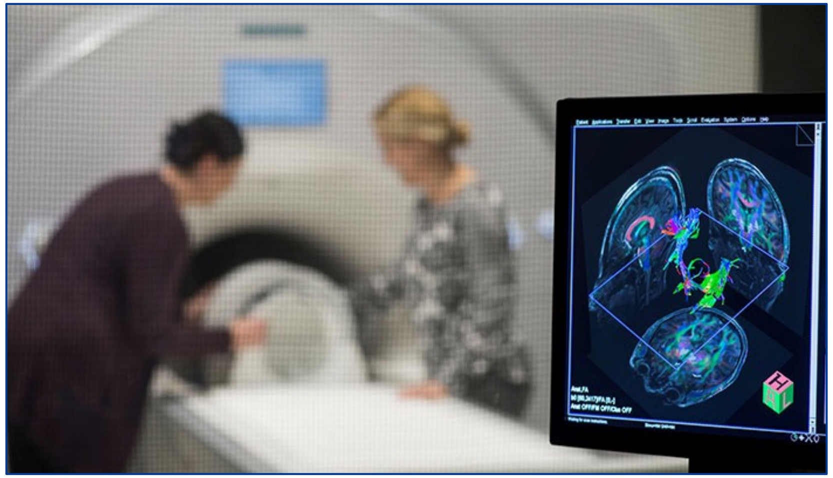
Exposure variables collected at day of life ~11 (timepoint 1) and day of life ~49 (timepoint 2):

Human milk samples analyzed for 19 most abundant HMOs via HPLC

Initial focus on concentrations of 2’FL, 3FL, 3’SL, and 6’SL

Outcome variables also collected at term-corrected age:

- Brain images obtained using a 3T MRI scanner
- Quantified brain volumes via Morphologically Adaptive Neonatal Tissue Segmentation software



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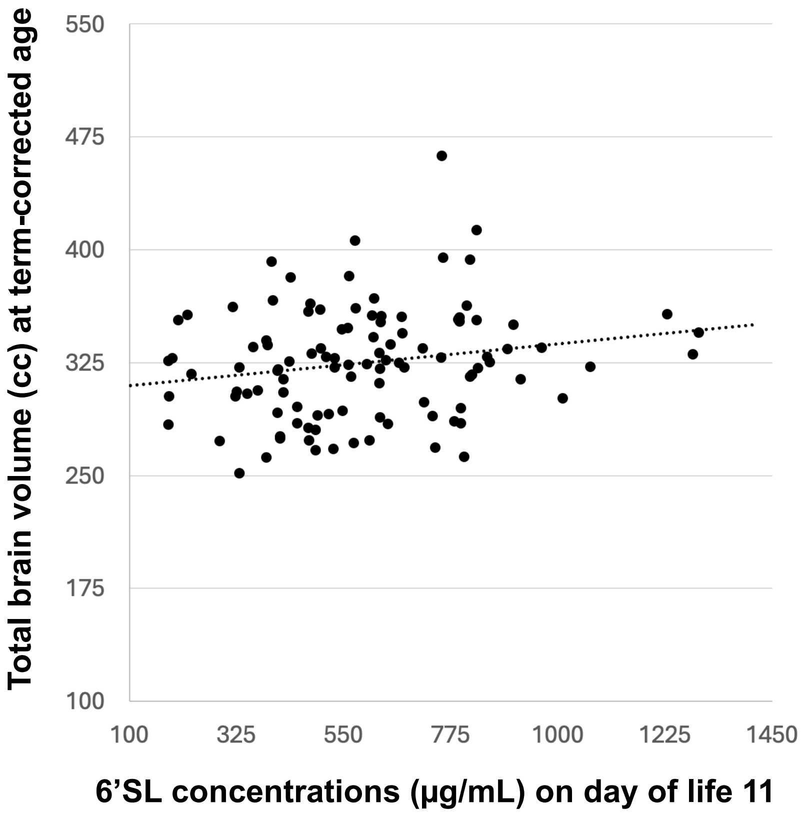
EXAMPLE OF PRELIMINARY RESULTS

Higher 6’SL concentrations on day of life 11 associated with larger total brain volume at term-corrected age

An increase of 100 µg/mL in 6’SL was associated with 4.6 cc (95% CI=1.1, 8.1) increase in total brain volume

Data suggest that greater 6’SL exposure may support brain growth during critical period of development

Fig. Association of 6’SL with total brain volume.



OVERALL SUMMARY

Human milk is a complex biological system with nutritive and bioactive roles in early brain development

Carbohydrates are a major constituent of human milk with distinct structures and diverse physiological functions

Fructose is a simple carbohydrate derived from maternal diet, may confer adverse effects on brain tissue microstructure and cognitive development

HMOs are complex carbohydrates with >200 distinct structural permutations, may confer beneficial effects on brain white matter myelination and dendritic arborization

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THANK YOU

Children's Hospital Los Angeles

Bradley Peterson, MD
Ravi Bansal, PhD
Siddhant Sawardekar, MS
Michael Goran, PhD

University of California, San Diego

Lars Bode, PhD

Boston Children's Hospital

- Banu Ahtam, MSc, Dphil
- Borjan Gagoski, PhD

Brigham and Women's Hospital

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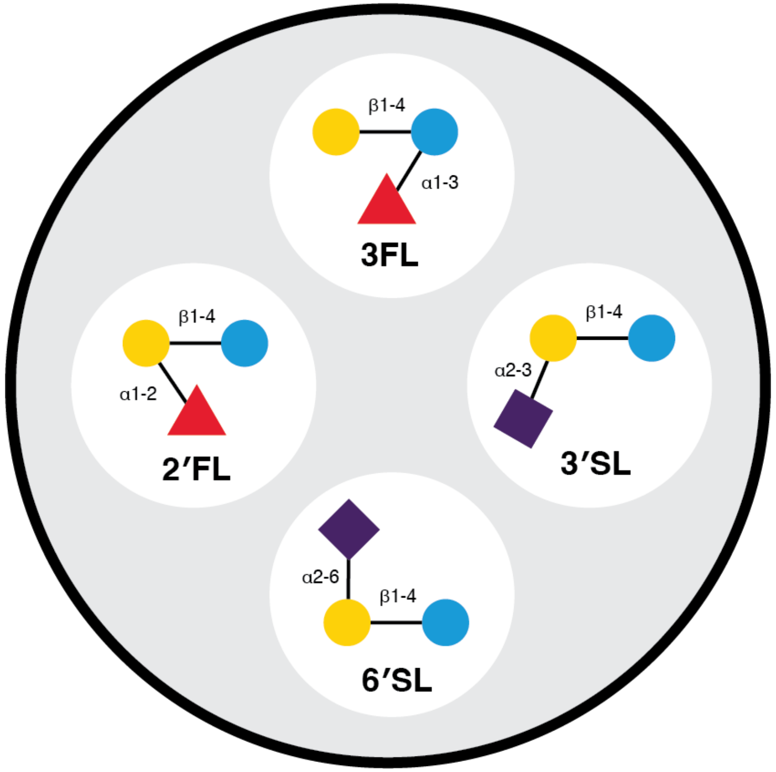

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Q&A

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