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FROM GUT TO BRAIN: THE ROLE OF FRUCTOOLIGOSACCHARIDES AND GALACTOOLIGOSACCHARIDES IN MODULATING THE GUT-BRAIN AXIS DURING EARLY CHILDHOOD

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Abstract

Background: The first five years of life are an essential stage during which the gut microbiota and the brain develop simultaneously. This development is mediated by the gut-brain axis (GBA), a bidirectional communication system operating through neural, endocrine, immune, and metabolic pathways. Fructooligosaccharides (FOS) and galactooligosaccharides (GOS) are well-researched prebiotics that promote beneficial gut bacteria producing neuroactive molecules such as short chain fatty acids, gamma-aminobutyric, and serotonin precursors, which are associated with neurotransmitter synthesis, blood-brain barrier function, HPA axis regulation, and neuroinflammation. **Methods**: This narrative review discusses the potential mechanisms by which FOS and GOS might affect gut-brain communication in early childhood, drawing from experimental animal studies and clinical trials in adults and children. **Results**: In animal models, FOS and GOS reduce anxiety and depression-like behaviors and may support cognitive function through SCFA-mediated effects on neurotransmitter modulation. Human pediatric evidence remains limited, though recent findings suggest GOS can lower emotional responsiveness and cortisol levels in school-age children. **Conclusion**: Important gaps remain, particularly the lack of long-term studies in children under five and insufficient data from low- and middle-income countries. Well-designed pediatric studies are needed to understand FOS and GOS effects on early brain development.

Keywords: prebiotics, fructooligosaccharides, galactooligosaccharides, gut-brain axis, early childhood

Introduction

One of the most dynamic stages in terms of development is early childhood that covers the period from birth until the fifth year of age. The brain experiences extensive maturation throughout this phase; the total brain volume grows by 101% in the first year of age, followed by 15% during the second year, reaching 80–90% of the adult volume at 2 years of age, encompassing critical neurodevelopmental processes including synaptogenesis, myelination, axonogenesis, neural pruning, and the establishment of functional neural circuits.[1,2] It is important to note that this period of intensive neurodevelopment overlaps with gut microbiota colonization and maturation, which provides a biologically sensitive period in terms of interactions between gut microbiota composition, nutrition, and neurodevelopment.[3,4]

The gut-brain axis refers to a complex bi-directional communication system that involves interactions between the gastrointestinal (GI) tract and the central nervous system (CNS), and the interaction takes place through neural, hormonal, immune, and humoral pathways.[5,6] The gut microbiome plays an important role in regulating the functioning of the GBA by releasing several neuro-active products, such as short-chain fatty acids (SCFAs), tryptophan-derived metabolites, and neurotransmitter precursors, such as gamma-aminobutyric acid (GABA) and serotonin, which influence brain development and behavior.[7,8] Imbalances in the gut microbiome during early stages of development may contribute to neurodevelopmental and cognitive issues and increase the risk of neuropsychiatric conditions such as autism and attention deficit hyperactivity disorder (ADHD).[4,9–11]

The prevalence of neurodevelopmental disorders (NDDs) in children around the globe highlights the need to find early-onset modifiable risk factors associated with these conditions. Information obtained through the Global Burden of Disease (GBD) 2021 studies conducted in 204 countries shows that prevalence rates for autistic spectrum disorder (ASD), ADHD, and intellectual disabilities in children aged between 0 and 14 years remains to be a significant public health concern.[12] Anxiety and depressive disorders have similarly been seen in young children, where origins can trace back to the prenatal/postnatal microbiome environment.[13] In light of this information, there is increased research on dietary approaches

that are capable of modulating the gut microbiome during early life to support optimal neurodevelopmental outcomes.

Fructooligosaccharides (FOS) and galactooligosaccharides (GOS) represent carbohydrate sources which cannot be digested and function as prebiotics. In recent years, FOS and GOS have been subject to intensive research for their applications in infant formulas and complementary foods. Both prebiotics have demonstrated selective effects on the stimulation of beneficial intestinal bacteria, such as Bifidobacterium and Lactobacillus species, and the synthesis of SCFAs during colonic fermentation.[14,15] Prebiotic-related changes affect more than just the digestive system; SCFAs play an important role in regulating blood-brain barrier permeability, neuroinflammation, and the synthesis of neurotransmitters including serotonin, dopamine, and GABA.[7,16] GOS has further been shown to enrich bacterial species capable of producing GABA and serotonin, as well as synthesize neuroactive metabolites involved in neurodevelopmental processes.[17,18] Additionally, FOS, through its bifidogenic and butyrogenic effects, has been associated with enhanced GABA concentrations in both the gut and brain in preclinical models.[19]

Despite such mechanistic plausibility, current research on FOS, GOS, and the gut-brain axis in young children remains fragmented. Pre-clinical data from animals, especially germ-free or antibiotic-infused rodents, while informative, present significant limitations for direct translation to human pediatric populations.[4,20] Meanwhile, most of the available human data has been generated from groups supplemented with infant formula in developed nations, with scarce consideration of the toddler and preschool stages (1-5 years), where microbial colonization advances and cognitive, executive, and social-emotional milestones, among others, are continuously established.[3,21] Moreover, there has yet to be an integrative narrative review that collates research regarding the gut-brain axis outcomes associated with early childhood, such as cognition, behavior, and psychological wellbeing, specifically within the context of FOS and GOS supplementation.

This review aims to address this gap by: (1) delineating mechanistic pathways of gut-brain communication; (2) reviewing microbiome-modulating properties of FOS and GOS; (3) evaluating preclinical and clinical evidence linking FOS/GOS to neurodevelopmental outcomes in young children; and (4) identifying key knowledge gaps and future research directions.

Methods

This narrative review was performed across PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar in April 2026, prioritizing English-language publications. This review does not follow the PRISMA systematic review methodology, as the objective was to provide a comprehensive and integrative synthesis of current knowledge rather than a systematic appraisal of all available evidence. Moreover, this review was restricted to articles written between the years 2004 and 2026. While most of the cited literature had been published after 2010, landmark papers published before 2010 were still considered for inclusion, particularly if they offered essential information that had yet to be replaced by newer research studies, like the initial investigation into microbiota-mediated HPA axis programming (Sudo et al.[22]) and the earliest large-scale MRI assessment of neonatal brain volume growth (Knickmeyer et al.[1]).

The search strategy employed combinations of key terms: ("fructooligosaccharides" OR "FOS") AND ("galactooligosaccharides" OR "GOS") AND ("gut-brain axis" OR "microbiota-gut-brain") AND ("children" OR "infant" OR "early childhood" OR "pediatric"). Additional searches used outcome-specific terms including "neurodevelopment," "cognition," "anxiety," "autism spectrum disorder," "GABA," "serotonin," "short-chain fatty acids," and "blood-brain barrier."

Studies were eligible if they: (1) examined FOS, GOS, or their combination as the primary prebiotic intervention; (2) investigated outcomes related to the gut-brain axis, including neurodevelopmental, cognitive, behavioral, emotional, or neurobiological endpoints; (3) included pediatric populations (0-18 years) or relevant preclinical models; and (4) were published in peer-reviewed journals. Studies were excluded if they focused exclusively on adult populations without relevance to pediatric mechanisms, or if they were editorials, conference abstracts, or non-peer-reviewed preprints. Adult studies were included only when providing foundational mechanistic evidence absent from pediatric literature, as direct human evidence in children aged 0-5 years is currently scarce for most gut-brain axis outcomes. Animal studies were included to provide mechanistic context, given that ethical and practical constraints limit invasive neurodevelopmental research in young children. The initial search yielded over 200 records; following title and abstract screening and full-text review by two authors, with duplicate removal prior to screening, a total of 50 references were included. No

formal risk-of-bias assessment or meta-analytic synthesis was performed, consistent with the narrative review design. To minimize selection bias, the authors prioritized high-impact peer-reviewed journals, systematic reviews, and landmark studies.

Result & Discussion

Communication Pathways

There are four mechanisms through which the gut-brain axis operates, which include: neural, endocrine, immune, and humoral.[5,22] The neural mechanism occurs mainly via the vagus nerve, since this nerve offers a direct anatomic connection between the enteric nervous system (ENS) and brainstem nuclei, especially the nucleus tractus solitarius (NTS).[23] Microbial metabolites activate vagal afferent nerves indirectly through enteroendocrine and enterochromaffin cells, thereby modulating neurotransmitter release that affects mood and cognitive activities.[23,24] The second mechanism concerns the endocrine pathway, centered on the hypothalamic-pituitary-adrenal (HPA) axis;germ-free mouse studies demonstrated that the absence of microbiota led to an exaggerated HPA stress response, which could be reversed through microbiome recolonization.[25] Cytokine production in gut-associated immune cells makes up for the immune mechanism; pro-inflammatory cytokines, like IL-1β, IL-6, and TNF-α, can compromise blood-brain barrier integrity and disrupt neuron functions.[24,26] Lastly, the humoral mechanism deals with the transport of microbially produced metabolites, such as SCFAs, tryptophan derivatives, and bile acids, through circulation to the brain.[5,22]

Key Neuroactive Metabolites Produced in the Gut

Acetate, propionate, and butyrate, collectively known as short-chain fatty acids (SCFAs), are derived from anaerobic fermentation of indigestible carbohydrates such as FOS and GOS.[14] Apart from being colonocyte energy sources, SCFAs have systemic functions; in animal studies, butyrate can pass through the blood-brain barrier and act as a neuroprotector by enhancing neuronal well-being, reducing oxidative stress, and regulating neurotransmitters.[7,16,27] It is estimated that about 90–95% of the body's serotonin is made by enterochromaffin cells in the gastrointestinal tract under microbial metabolite regulation.[23,28] It is important to note that gut-derived serotonin does not cross the blood-brain directly; rather, it may influence central

nervous system function indirectly through activation of vagal afferent pathways, modulation of immune signaling, and regulation of tryptophan availability for central serotonin synthesis.[23,29] Some gut microbes like Lactobacillus and Bifidobacterium species can directly produce GABA by converting glutamate via enzymatic reactions.[30] Lastly, the tryptophan-kynurenine pathway provides an additional nexus of gut-brain communication, generating both neuroprotective and neurotoxic metabolites implicated in depression, anxiety, and neurodevelopmental disorders.[8,29]

Early Childhood as a Critical Window

The concurrence of rapid brain development and gut microbiome colonization during the first 1,000 days of life and beyond creates a biologically unique period of vulnerability and opportunity.[3,31] During this window, key neurodevelopmental processes, such as neurogenesis, synaptogenesis, myelination, neural pruning, microglia activation, and blood-brain barrier maturation, taking place simultaneously as the gut microbiome transitions from the relatively simple maternal seeding to a complex microbiome that can perform many functions.[3,4,32] Preclinical studies demonstrate that microbiome disruption during specific early-life windows, particularly the weaning period, produces enduring effects on brain function and behavior persisting into adulthood.[4,32,33] In human populations, dietary transitions from exclusive milk feeding to complementary foods profoundly reshape the gut microbial composition, representing natural intervention points for prebiotic supplementation.[9,34]

FOS and GOS: Properties and Gastrointestinal Mechanisms

FOS consists of fructose chains linked by β(2→1) bonds (scFOS, DP 2–4; lcFOS, DP 10–60), while GOS comprises galactose chains (DP 2–8) linked by β(1→4) or β(1→6) bonds.[14,17] Both FOS and GOS resist enzymatic hydrolysis in the upper gastrointestinal tract and reach the colon intact, where they undergo selective fermentation by indigenous microbiota.[14,15] The fermentation process generates SCFAs, predominantly acetate, propionate, and butyrate, as well as lactate and gases. The chain length of the oligosaccharide influences fermentation kinetics: shorter-chain GOS and scFOS are fermented more rapidly in the proximal colon, while longer-chain variants provide sustained prebiotic activity extending to the distal colon.[17]

Cross-feeding interactions between primary fermenters (such as *Bifidobacterium* producing lactate) and secondary fermenters (which convert lactate to butyrate) further amplify the metabolic output of prebiotic fermentation and contribute to the diversity and functional complexity of the gut ecosystem.[17] In infant formula trials, GOS/FOS supplementation (9:1 ratio) produces gut microbiota profiles approximating those of breastfed infants, with higher *Bifidobacterium* proportions and lower pathogenic colonization.[34–36] GOS supplementation has also been associated with enrichment of mucin-degrading bacteria with roles in gut barrier function.[37]

In addition, the use of pediatric GOS/FOS supplementation has been associated with improved stool characteristics, increased SCFA production, elevated secretory IgA levels, and reduced risk of GI and upper respiratory tract infections.[35,38–41] More importantly, maintenance of the barrier function of the gut due to increased production of butyrate leads to increased production of tight junction proteins and prevention of transport of bacterial endotoxins that cause inflammation and blood-brain barrier disruption.[16,26,27] These GI-level effects constitute the mechanistic foundation of the gut-brain axis hypothesis: neuroactive metabolites produced through prebiotic fermentation must traverse an intact intestinal barrier to reach the brain.

FOS, GOS, and the Gut-Brain Axis in Early Childhood

Modulation of neurotransmitter signaling pathways via microbiome-mediated mechanisms by FOS and GOS forms the backbone of the gut-brain axis theory. Fermentation of GOS encourages the growth of bacteria capable of producing GABA and serotonin, which are essential in regulating anxiety and maintaining emotional balance, along with increasing the formation of SCFAs that possess neuroactive qualities. [17,18] Since GABA acts as the main inhibitory neurotransmitter within the brain, it is essential when it comes to prebiotic supplementation. In an animal study, FOS elevated the amount of GABA produced in both the gut and brain of adolescent mice by altering the composition of gut microbiota, whereby the concentration of GABA in the gut correlated with the concentrations of GABA and homocarnosine level in the brain, which represents the first evidence directly linking dietary prebiotics to central GABA changes.[19]

Moreover, serotonin is yet another neuroactive molecule that prebiotics can target. Studies have indicated that microbiome-derived SCFAs stimulate the formation of serotonin within the colon via their impact on enterochromaffin cells.[28] Considering that serotonin produced by the gut innervates vagal nerve fibers and sends messages to brain stem nuclei regulating mood and stress responses[23], the effect of prebiotics on serotonin production may influence emotional and cognitive outcomes in the long run. Moreover, butyrate has been found to pass through the blood-brain barrier and exhibit neuroprotection.[7,16]

In animal studies, chronic administration of FOS, GOS, or FOS+GOS increased cognitive function and decreased anxiety-related behavior, which was associated with alterations in SCFA production in the cecum and changes in hippocampal gene expression profiles.[42] Likewise, in a preclinical model, dietary administration of scGOS:lcFOS from birth in BALB/c mice increased social behavior and decreased anxiety, which was associated with alterations in serotonin metabolism in the prefrontal cortex.[43] In a human clinical trial, a randomized controlled trial indicated that 4-week supplementation with GOS (5.5 g/day) in 6- to 14-year-old children reduced anxiety and depression levels.[44]

Furthermore, in an animal model, FOS+GOS reduced chronic stress-induced corticosterone elevations, pro-inflammatory cytokines, and depression/anxiety-like behaviors while normalizing stress-induced microbiota perturbations.[42] Additionally, in high-fat diet-fed mice, FOS and GOS reversed anxiety and depression, reduced neuroinflammation, and promoted elevated brain acetate and GPR43 levels.[45] In a clinical trial involving healthy adults, a 3-week B-GOS supplementation lowered salivary cortisol awakening response and decreased attentional vigilance toward negative stimuli in healthy adults, highlighting differential psychobiological properties between these prebiotics.[46] A pediatric trial confirmed these anxiolytic effects extend to children[38], though replication in the 0–5 year window remains needed.

The gut-brain axis has attracted considerable attention in the context of neurodevelopmental disorders, particularly ASD and ADHD, for which gut dysbiosis has been consistently documented. ASD children suffer about 55% prevalence of GI disorders and disturbances in gut bacterial populations.[47] In the valproic acid-induced mouse model, GOS/FOS mixture at a ratio of 9/1 from birth corrected bacteria taxa, repaired leaky gut

syndrome, improved immune response balance, inhibited cerebellar inflammation, and enhanced social skills and cognition.[48,49] In a human clinical trial, Grimaldi et al. demonstrated that B-GOS positively influenced GI symptoms and social abilities of autistic children[43]; however, a subsequent trial by Palmer et al. showed less consistent results, with no significant changes in overall GI outcomes although a reduction in the proportion of children with severe GI symptoms was observed.[50] Meta-analysis has suggested that younger patients may benefit more from microbiome-targeting strategies and ADHD may have better clinical outcomes than ASD.[51,52] Controlled human prebiotic intervention studies in ADHD are almost non-existent. This represents one of the most significant gaps in the current literature.

In animal studies, SCFAs, particularly butyrate, have been shown to maintain blood-brain barrier integrity by decreasing paracellular permeability through reconstitution of proteins in the junctional complexes.[53,54] According to Zemmel et al., the development of the blood-brain barrier and cognitive function is controlled by early-life gut microbiome maturation within a gnotobiotic mouse model.[53] While it is biologically plausible that FOS and GOS contribute to blood-brain barrier protection through butyrate production, no direct human research exists on the effects of prebiotics in this regard.

Current Evidence: Human Studies vs. Preclinical Data

The evidence base linking FOS and GOS to gut-brain axis modulation in early childhood is characterized by a marked asymmetry between robust preclinical data and limited human clinical evidence. However, it is important to recognize that the current body of evidence contains a number of notable methodological limitations. For example, most human clinical trials with children have used relatively small numbers of patients, very short study periods (usually between 4-12 weeks), and different types of FOS and GOS in various combinations and dosages. Neurodevelopmental markers used for comparison are not standardized between studies, and the microbiome assessment techniques vary considerably, making direct comparisons difficult. Additionally, the confounding effects of overall infant formula composition make it more challenging to isolate the specific effects of FOS and GOS. These limitations should be considered when interpreting the evidence summarized in Table 1.

Table 1. Summary of evidence for FOS/GOS effects on gut-brain axis outcomes

Domain	Evidence from Animal Studies	Evidence from Human Studies	Key Evidence Gap
Neurotransmitter modulation (GABA, serotonin)	FOS increases gut and brain GABA[16]; GOS promotes GABA-and serotonin-producing bacteria[14,15]	B-GOS reduces cortisol awakening response and shifts emotional bias[46]; very limited indirect evidence from formula trials	Longitudinal pediatric studies with neurochemical biomarkers
Cognition and attention	Enhanced memory, reduced anxiety-like behavior in mice[42,43]	Improved emotional control in school-aged children[44]	RCTs in children 0–5 years with validated cognitive endpoints
Stress, anxiety, mood	FOS+GOS reduces corticosterone, pro-inflammatory cytokines, and depression/anxiety-like behaviors in mice[42,45]	B-GOS reduces cortisol and emotional vigilance to negative stimuli[46]; GOS reduces trait anxiety and depression in children 6–14 years[44]	Pediatric stress/anxiety trials in the 0–5 year window
ASD	GOS/FOS (9:1) normalizes microbiota, reduces neuroinflammation, improves social behavior in VPA model[48]	B-GOS improves GI symptoms and social behavior in children with ASD[49]; inconsistent results in subsequent trial[50]	Controlled FOS/GOS-specific trials in young children with ASD
ADHD	Growing mechanistic evidence from dysbiosis studies	No controlled prebiotic trials available	Controlled prebiotic trials in children with ADHD

Domain	Evidence from Animal Studies	Evidence from Human Studies	Key Evidence Gap
BBB Integrity	SCFA restores BBB in germ-free models; microbiome maturity regulates BBB development[53,54]	No direct human evidence available	Direct measures of BBB function in prebiotic-supplemented children

Note: Evidence classification is based on qualitative assessment of the number, consistency, and methodological rigor of available studies. "Evidence from Animal Studies" refers to findings from in vivo rodent models; "Evidence from Human Studies" includes both adult and pediatric clinical trials where specified. The absence of evidence does not imply absence of effect.

From a practical standpoint, FOS and GOS are already widely incorporated into commercially available infant formulas, typically at a 9:1 scGOS:lcFOS ratio of concentrations of 0.6-0.8g/dL, and have demonstrated a favorable safety profile in pediatric populations.[32,35] Both prebiotics are generally recognized as safe (GRAS) and are approved for use in infant nutrition by major regulatory authorities. The existing evidence on the beneficial effects of the prebiotics on the gastrointestinal tract health among infants could lay the groundwork for exploring the neurodevelopmental effects of the two prebiotics as well.[55,56] However, extending these findings to low- and middle-income countries (LMIC) presents additional challenges, as children in these settings face different conditions including malnutrition, recurrent enteric infections, and low dietary diversity that may modify the prebiotic response.[57]

Schematic illustration of the gut-brain axis pathways modulated by FOS and GOS supplementation in early childhood is presented in Figure 1. FOS and GOS undergo selective fermentation by beneficial gut microbiota (Bifidobacterium and Lactobacillus), producing SCFAs, GABA, and serotonin precursors. These metabolites affect brain development through four major communication pathways: (1) neural pathway via vagus nerve activation; (2) endocrine pathway via HPA axis modulation; (3) immune pathway via cytokine regulation; and

(4) humoral pathway via systemic metabolite transport. Arrows indicate the direction of signaling between components.

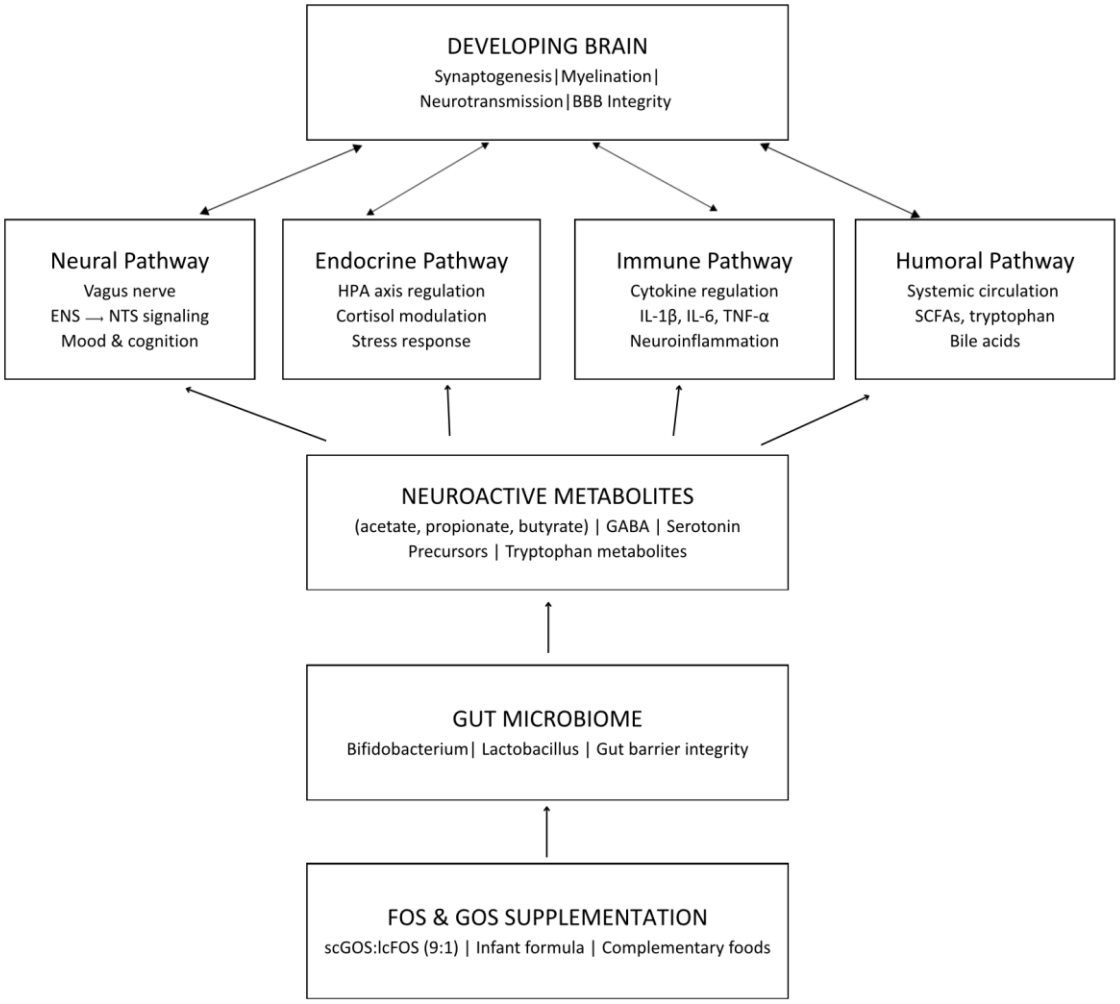

Figure 1. Gut-Brain Axis Pathways Modulated by FOS & GOS in Early Childhood

Conclusion

This review found that current evidence supports a mechanistic link between FOS and GOS supplementation, gut microbiome modulation, and gut-brain axis signaling, though the strength of evidence differs considerably between preclinical and clinical conditions. Preclinical studies have documented a variety of beneficial actions, including anxiolytic, improved cognitive functions, decreased HPA axis responsiveness, reduced neuroinflammation, and improved integrity of the BBB. Preliminary evidence from humans

suggests that GOS can lower cortisol responsiveness and anxiety behavior in both adults and young school-age children. Nevertheless, the crucial 0-to-5-year period still suffers from a significant lack of exploration in clinical studies.

Some of the key gaps are lack of longitudinal randomized controlled trials using validated neurodevelopmental endpoints within the 0-5-year age range, inadequate research on the complementary feeding (between 6-24 months), inadequacy of research of investigation of the role of sex differences and ideal FOS:GOS ratios, insufficient research conducted among LMIC countries, and lack of omics data to prove causal relationship. Both FOS and GOS are safe and omnipresents, they are considered as good options in developing early life nutrition interventions to support brain development via gut pathways. Although causality has not been demonstrated in humans, clinical trials are imperative.

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Conflict of Interest

There is no conflict of interest in this publication.

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