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DEVELOPMENT OF THE PEDIATRIC GUT MICROBIOME: IMPACT ON HEALTH AND DISEASE

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Abstract

The intestinal microbiota are important in proper human growth and development before and after birth, during infancy and childhood. Microbial composition may yield insights into the temporal development of microbial communities and vulnerabilities to disorders of microbial ecology such as recurrent *Clostridium difficile* infection. Discoveries of key microbiome features of carbohydrate and amino acid metabolism are lending new insights into possible new therapies or preventative strategies for inflammatory bowel disease (IBD) and irritable bowel syndrome (IBS). In this review, we summarize the current understanding of the development of the pediatric gastrointestinal microbiome, the influence of the microbiome on the developing brain through the gut-brain axis, and the impact of dysbiosis on the development of disease. Microbial dysbiosis will be explored in the context of pediatric allergy and asthma, recurrent *C. difficile* infection, IBD, IBS, and metabolic disorders. The central premise is that the human intestinal microbiome plays a vital role throughout human life beginning in the prenatal period and extending throughout childhood in health and disease.

Keywords

children; early life; gut-brain axis; gut microbes; microbiota; neonatal

INTRODUCTION

The human intestine harbors trillions of microbial cells which form a symbiotic relationship with the host and play a vital role in both health and disease. While the specific microbial composition varies among healthy individuals, the functional repertoire of the microbiome is conserved[1]. These microbes play important roles in mammalian homeostasis, including

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providing essential nutrients[2, 3], metabolizing dietary fiber into short chain fatty acids[4], and ensuring proper development of the immune system[5]. Therefore, the gut microbiota is considered a crucial factor for proper early life development and lifelong health. However, when the balance of the intestinal microbiota becomes disrupted, alterations can lead to immunologic dysregulation and the development of diseases including *Clostridium difficile* infection[6], inflammatory bowel disease[7, 8], irritable bowel syndrome[9, 10], asthma[11], obesity[12], and neurodevelopmental disorders such as autism[13]. In this review, we describe the development of the pediatric microbiome, starting *in utero* and progressing through infancy, childhood and adolescence. We then discuss the impact of the microbiome on the developing brain and neural function through the gut-brain axis. We conclude with a discussion on the impact of dysbiosis on disease development.

ESTABLISHMENT OF EARLY LIFE INTESTINAL MICROBIOME

Microbial Colonization of the Neonatal Gut

For many years it was believed that the fetus' in utero environment was sterile, with infant gut colonization beginning at the time of delivery. However, recent work demonstrating the presence of a microbial community in the meconium[14, 15] has challenged this notion. While still controversial[16], it is now clear that microbial colonization of the infant gut may begin prior to birth as additional evidence suggests microbial colonization of the placenta[17, 18], amniotic fluid[19, 20], and the umbilical cord[21]. Aagaard *et al*[17] collected 320 placental specimens under sterile conditions and found a unique placental microbiome niche, which most closely resembled the human oral microbiome[17]. Furthermore, a randomized, double blind, placebo-controlled trial demonstrated that maternal probiotic supplementation could affect the expression of Toll-like receptor (TLR)-related genes in both the placenta and the fetal intestine.[19] This finding suggested that the fetal intestinal immune gene expression profile could be affected by microbial contact *in utero*. Similarities between the unique microbiota composition of the placenta and amniotic fluid to that of the infant meconium further suggests a prenatal microbial transfer from mother to fetus.[22] Importantly, variations in the placental microbiome have been shown to associate with preterm birth[17] as well as low birth weight in full term infants.[18]

In addition to potential in utero environmental influences, many factors have been found to contribute to early intestinal colonization, such as gestational age at birth. Studies have shown that the intestinal microbiota of preterm infants differs from that of healthy term infants[23], with preterm infant microbiomes being dominated by *Enterobacter, Staphylococcus,* and *Enterococcus*[24, 25]. Prematurity is associated with a high risk for neonatal complications and can lead to significant morbidity and mortality[26]. These premature neonates are often exposed to prolonged hospitalizations, antibiotics, and formula feeding which may all disrupt the maturation of health-associated microbial communities[27]. Importantly, alterations in the microbiome of preterm infants have been correlated with increased risk for complications such a necrotizing enterocolitis[28, 29] and late-onset sepsis[30, 31].

Another major influence on the infant gut microbiome is infant diet. Breast-fed infants have microbiota enriched in *Lactobacillus, Staphylococcus, and Bifidobacterium*, as compared to

formula-fed infants with microbiomes dominated by *Roseburia, Clostridium,* and *Anaerostipes*[32]. Formula-fed infants have greater quantities of microbes associated with inflammation, with a more rapid maturation of their microbiome toward that of an adult-type composition[27, 32–34]. Conversely, studies have shown that human milk isolates contain symbiotic and potentially probiotic microbes[32, 33]. Human milk oligosaccharides, the 3rd largest component in human milk, are considered prebiotic, with antimicrobial and antiadhesive properties thought to be protective to the infant[35–38]. Interestingly, breast-fed infants have reduced microbial diversity than their formula-fed counterparts[39]. However, this reduced diversity is associated with an increase in genes relevant for degradation of human milk oligosaccharides (HMOs)[39]. HMOs, in turn, are able to amplify the presence of specific bacterial populations in the infant gut[35].

Development of the infant intestinal microbiota

During the first year of an infant's life, the relatively simple neonatal microbiome matures and develops into a more complex microbiome, with a composition more representative of an adult gastrointestinal tract enriched in *Bacteroides* and *Firmicutes*[32, 40]. During the first year of life, the infant's microbiome also gains functionality similar to their mother's gut metagenome, with decreasing inter-individual variation over time[32, 40]. An increased number of bacterial genes relevant for plant polysaccharide metabolism primes the infant microbiome for the adult diet even before the introduction of solid foods[41]. Once solid foods are introduced, there is a sustained shift in the microbial composition with an increase in *Bacteroidetes*. Additional modifications include increased short chain fatty acids in the stool, and expression of genes relevant for carbohydrate metabolism, vitamin biosynthesis, and xenobiotic degredation[41].

During the early infant development period many exposures can influence the progression of the intestinal microbiota. For example, antibiotic treatment during this period of early life development can dramatically alter the intestinal microbiota structure[40–42]. Similarly, exposure to less sanitary environments, including contact with household pets and siblings, have significant effects on the developing microbiome[42, 43]. In fact, the number of older siblings positively correlates with bacterial diversity and richness at 18 months of age, with increasing relative abundances of *Firmicutes* and *Bacteroidetes* in infants with more siblings[44].

Conversely, the microbiome also affects the general health status of the infant or child. A longitudinal comparative study of Malawian twins discordant for kwashiorkor found that the malnourished twin displayed abnormal microbiome signatures compared to the healthy twin[45]. As proof of concept that the microbiome was a causal factor in the development of kwashiorkor phenotype, frozen fecal communities from the discordant twin pairs were transplanted into gnotobiotic mice. The mice receiving kwashiorkor microbiome exhibited marked weight loss with accompanied perturbations in amino acid, carbohydrate and intermediary metabolism[45].

Development of pediatric and adolescent intestinal microbiota

While some investigators have suggested that the pediatric microbiome reaches a relatively stable, adult-like configuration within the first 3 years of life[32, 46], other studies have demonstrated continued development through childhood into the teenage years[47–49]. In a study comparing the intestinal microbiota of 1–4 year old children to heathy adults, the adult microbiome had significantly greater diversity (abundance and richness) than young children[48]. At the phylum-like level, the predominant bacterial groups were similar, including *Firmicutes*, *Bacteroidetes* and *Actinobacteria*[48]. However, at the genus level, multiple phylogenetic groups were significantly different between the children and adult populations[48].

A study comparing the fecal microbiota of adolescents (11–18 years of age) to healthy adults found that the number of detected species were similar between groups, but the relative abundances of genera differentiated adolescents from adults, suggesting that the microbiomes differed, even into adolescence[49]. Hollister et al[47] compared 7–12 year old children to adults, and found that similar to adults, the pediatric gut microbiome was largely composed of *Bacteroidetes* and *Firmicutes* (Figure 1). However, the relative abundances of these bacteria differed from adults, with relatively lesser abundances of *Bacteroidetes* and greater abundances of *Firmicutes* and *Actinobacteria*[47]. They also found that while many taxa were shared between pediatric and adult samples, the distribution was significantly different, with children having greater abundances of bacteria belonging to the genera *Faecalibacterium, Dialister, Roseburia, Ruminococcus,* and *Bifidobacterium*[47].

Importantly, Hollister et al[47] also characterized the metagenomic profiles of pediatric and adult microbiomes. Children demonstrated an enrichment of genes which may support ongoing development, including genes involved in vitamin synthesis, de novo folate synthesis, and amino acid metabolism[47]. Meanwhile, adults were enriched in pathways previously linked to inflammation, including genes involved in oxidative phosphorylation, lipopolysaccharide biosynthesis, flagellar assembly, and steroid hormone biosynthesis[47]. While the intestinal communities of children shared 35–46% similarity to each other taxonomically, they had substantially greater overlap at the functional level, with >90% similarity of the ortholog group and pathway levels[47]. This difference implies that the functional capacity of microbes present in the pediatric gastrointestinal tract is more highly conserved than microbial composition.

THE GUT-BRAIN AXIS

Impact on brain development

The human brain undergoes rapid growth during the perinatal period, corresponding to dramatic changes in the maternal microbiota[50]. Mothers demonstrate an increase in Proteobacteria and Actinobacteria, and a decreased richness as they progress from the first to the third trimester of pregnancy[50]. While these changes are often correlated with metabolic syndrome in nonpregnant females, in the setting of pregnancy these changes are beneficial in promoting energy storage and allowing for adequate growth of the fetus[50].

Many studies have demonstrated the importance of the microbiota during brain development, including the microbiome's indirect effect on tryptophan metabolism and serotonin (5-HT) synthesis (Figure 2). 5-HT is known to be crucial to CNS development[51]. Knock-in mice lacking the tryptophan hydroxylase 2 gene, demonstrated that a lack of brain 5-HT caused improper wiring of the brain that may lead to long-term changes and neurodevelopmental disorders[51]. When compared to specific pathogen free (SPF) mice, germ-free mice have increased motor activity and decreased anxiety, as well as altered levels of neurotransmitters such as noradrenaline, dopamine and 5-HT[52]. Importantly, these abnormalities can be prevented by exposing the mice to gut microbiota early in life[52]. Germ-free mice also have a decreased kynurenine:tryptophan ratio compared to conventionally raised mice, which normalizes upon exposure to gut microbiota immediately after weaning[53]. Similarly, aberrant anxiety responses were corrected with bacterial colonization of the gut in these animals[53]. Furthermore, rats treated with *Bifidobacterium infantis* showed reduced 5-HIAA concentrations in the frontal cortex, and increased plasma concentrations of tryptophan and kynurenic acid compared to controls[54]. Gut bacteria can also have direct effects on the metabolism and synthesis of tryptophan and 5-HT[55]. For example, there is *in vitro* evidence that some bacterial strains can produce 5-HT from tryptophan[55]. Meanwhile, some bacteria are able to synthesize tryptophan using enzymes such as tryptophan synthase[56, 57], while others degrade tryptophan with tryptophanase enzyme[57, 58].

Colonic bacteria have an important role of fermenting carbohydrates and proteins to produce metabolites, including short chain fatty acids (SCFA), which are essential for human health[4]. Erny *et al* determined that SCFA regulate microglial homeostasis[59]. Therefore, defective microglia were found in mice with altered microbiota, including germ-free mice, mice with temporal eradication of microbiota, and mice with limited microbial complexity[59]. Exposure to an indigenous microbiota during early development is also crucial for the development of a normal hypothalamic-pituitary-adrenal (HPA) system[60]. Germ-free mice display an exaggerated HPA stress response, which was reversible with exposure to specific pathogen-free (SPF) feces during early development[60]. However, reconstitution with SPF feces at a later developmental stage was ineffective at reducing the aberrant stress response[60]. This study demonstrates the important role that the microbiota play during early postnatal brain development, while brain plasticity may still be preserved.

Bidirectional gut-brain axis and its impact on brain function

The brain-gut-microbiota axis is a complex interplay between the CNS, the neuroendocrine and neuroimmune systems, the sympathetic and parasympathetic arms of the autonomic nervous system, the enteric nervous system, and the microbiota[10]. The communication throughout this axis is bidirectional, with brain signals affecting gastrointestinal tract motor, sensory and secretory functions, and simultaneous visceral signaling from the GI tract affecting brain function[61] (Figure 2).

Long-term treatment with the probiotic *L. rhamnosus* (JB-1) led to decreased levels of stressinduced corticosteroids, depressive symptoms, and anxiety[62]. Treatment with *L. rhamnosus* also induced region-specific alterations in expression of $GABA_{B1b}$ and $GABA_{A\alpha2}$[62]. Alterations in GABA expression are implicated in depression and anxiety

disorders. Importantly these changes were not found in vagotomized mice, implicating the vagus nerve as a direct line of communication between the gut bacteria and the brain[62].

Another study has implicated the gut microbiome in pain perception. Certain strains of *Lactobacillus* induce increased expression of μ-opioid and cannabinoid receptors in intestinal epithelial cells, mimicking the analgesic effects of morphine[63].

Similarly, the brain can affect the composition of the gut microbiota. These effects on the microbiota can be indirect, through changes in motility and secretion, or direct, through signaling molecules released into the gastrointestinal tract via enterochromaffin cells, neurons, and immune cells[64]. The autonomic nervous system (ANS) affects motility as well as mucus secretion into the gut lumen, both of which can alter the gastrointestinal environment, thereby changing the bacteria that are present[65, 66]. The ANS can also affect epithelial mechanisms involved in immune activation of the gut[64]. For example, exposure to stressful stimuli has been shown to increase permeability of the epithelium, allowing bacterial antigens to cross the epithelium and stimulate an immune response in the mucosa, which in turn alters the microbiome[67]. This increased permeability is secondary to mast cell degranulation, overproduction of interferon-γ, and decreased expression of mRNA encoding tight junction proteins[68].

DYSBIOSIS AND DISEASE

While it is clear that the maintenance of the microbiome is vital for preservation of health, imbalances in the microbiome can shift the microbiome-host relationship from symbiotic to pathogenic. Below, we discuss some examples of communicable and noncommunicable disorders that are associated with a dysbiotic microbiome.

Clostridium difficile Infection

Clostridium difficile infection (CDI) is the leading nosocomial infection in the United States, affecting more than 500,000 people annually[69]. A complex microbial community in the intestine is vitally important to providing colonization resistance to CDI. Therefore, alterations to the microbiota increases the risk of infection from *C. difficile*. When comparing patients with CDI to diarrheal and nondiarrheal controls, Schubert *et al*[6] determined that *Ruminococcaceae, Lachnospiraceae, Bacteroides* and *Porphyromonadaceae* were absent in patients with CDI, but highly associated with nondiarrheal controls. These compositional changes are even more pronounced in patients with recurrent CDI who have been exposed to multiple courses of antbiotics[70]. Recurrent CDI leads to increased abundance of *Proteobacteria*, with decreased abundances of *Bacteroides* and *Firmicutes* compared to healthy controls[71].

Antibiotic use is the most common risk factor for the development of CDI, with often longlasting changes to the microbiota[72]. These antibiotic-related changes included decreased taxonomic and functional diversity of the gut microbiome as well as a decreased colonization resistance against invading pathogens[73]. Additionally, Denève *et al*[74] discovered that exposure to subinhibitory concentrations of certain antibiotics upregulated

the expression of genes encoding colonization factors in *C. difficile*, and increased the adherence of *C. difficile* to cultured cells.

Proton pump inhibitor (PPI) use also increases the risk of CDI[75]. PPI use has been shown to alter the gut microbiota by decreasing microbial diversity, and decreasing the abundances of commensal microorganisms[76, 77]. Chronic PPI use leads to decreased abundances of *Bacteroidetes* and increased abundances of *Firmicutes* at the phylum level, which may predispose patients to CDI[78]. PPIs also increase fecal *Enterococcaceae* and *Streptococcaceae*, taxa which have been associated with CDI[77, 79].

Therapies aimed at correcting and restoring health-associated complex microbial communities have yielded successful outcomes in treating CDI. Fecal microbiota transplantation (FMT) is around 90% effective at curing recurrent CDI with one or more infusions[80]. The rationale behind FMT for CDI is that restoration of the fecal community structure could also restore function, including colonization resistance[81]. Weingarden et al[71] demonstrated that FMT normalizes both bacterial community composition and metabolic capacity. Pre-FMT fecal samples had greater concentrations of primary bile acids and bile salts, while post-FMT samples contained mostly secondary bile acids[71]. Patients with recurrent CDI yielded disrupted abilities to convert primary bile acids to secondary bile acids. Primary bile acids have been shown to promote germination and growth of *C. difficile*, while secondary bile acids inhibit this growth[82, 83]. Therefore, it is possible that the correction of bile acid metabolism, and not just restoration of community structure, is a crucial mechanistic element in the efficacy of FMT against CDI[71].

Inflammatory bowel disease

Inflammatory bowel disease (IBD), including Crohn's disease and ulcerative colitis, are also associated with a dysbiotic microbiome[7, 8]. However, it is unclear if this dysbiosis plays a role in the etiology of the disease, is a result of the disease, or both. Patients with IBD demonstrated exaggerated immune responses against commensal intestinal microbes, which may be essential for the development of intestinal inflammation[84, 85]. However, others theorize that an aberrant intestinal microbiota is the primary driver of inflammation in IBD[86]. In support of this theory, studies have shown that treatment with antibiotics can substantially decrease intestinal inflammation and improve IBD symptoms[87]. Also, many microbes which are enriched in IBD may be able to potentiate disease[88]. For example, Ohkusa et al[89] demonstrated that the abundance of *Fusobacterium* species is increased in patients with ulcerative colitis compared with healthy controls. In a separate study, Ohkusa et al[90] showed that when given as an enema, the isolated human strain of *Fusobacterium varium* caused UC-like colonic ulcerations in mice, indicating that this bacterium may play a role in the pathogenesis of ulcerative colitis.

Patients with IBD have a variety of changes in the fecal microbiota including decreased abundances of *Bacteroides, Firmicutes*, *Clostridia*, *Bifidobacterium* and *Lactobacillus,* as well as increased abundances of *Fusobacterium* and adherent-invasive *Escherichia coli*[88, 91, 92]. Patients with IBD have reduced diversity of the microbiome, which becomes more pronounced in inflamed as compared to noninflamed tissue[93]. Additionally, the functional composition of the gut microbiota is altered in IBD, with one study showing an

alteration of 12% of pathways analyzed compared to 2% of genera between IBD and healthy individuals[94]. Functional alterations in IBD patients include diminished carbohydrate metabolism and decreased production of butyrate and other short chain fatty acids[88, 94, 95].

Given the importance of the microbiome in IBD, therapies aimed at manipulating the microbiome have gained popularity. While there are some promising studies demonstrating the efficacy of certain antibiotic combinations in treating IBD, more controlled trials are needed[96]. Similarly, while studies exploring the use of probiotics in IBD have yielded encouraging results, results vary across studies and more randomized controlled trials are needed[97–99]. Finally, fecal microbiota transplantation (FMT) is a possible therapy for IBD, given its success in treating recurrent *C. difficile* infection[100]. Few randomized controlled trials have been conducted in patients with IBD, with varying results[101–104], and more controlled trials are needed to fully understand the therapeutic potential of FMT for the treatment of IBD.

Irritable Bowel Syndrome

Evidence for the microbiome's influence on disease is found in irritable bowel syndrome (IBS)[9, 10]. IBS is diagnosed based on the presence of chronic recurrent abdominal pain related to defecation or associated with changes in frequency or form of stool, without accompanying warning signs[105]. Multiple studies have demonstrated differences in the fecal microbial communities of patients with IBS compared to healthy controls[106]. Patient with IBS show reductions in the relative abundance of *Bifidobacterium* and *Lactobacillus*, as well as increased abundances in the *Firmicutes*:*Bacteroidetes* ratio[9, 107]. Similarly, a small number of studies have shown shifts in the small intestinal microbiota in patients with IBS[108], including evidence that small intestinal bacterial overgrowth may play a role[109]. While the majority of work has been done in adults with IBS, Saulnier *et al*[110] confirmed differences in microbiome signatures in pediatric IBS compared to healthy controls. Additionally, they were able to classify different subtypes of IBS using a limited set of discriminatory species, with a success rate of 98.5%[110].

Further support for the role of gut microbiome perturbations in the development of IBS is the persistence of IBS-like symptoms following confirmed bacterial or viral gastroenteritis, a term called post-infectious IBS[111]. Proposed mechanisms for post-infectious IBS include enteroendocrine cell hyperplasia, elevated T-lymphocytes, and increased gut permeability following infection[112, 113].

To further elucidate the role of the intestinal microbiota in IBS, multiple studies have examined the effects of probiotic supplementation in this disorder. Based on several meta-analyses and systematic reviews, probiotic use for treatment of IBS appears more effective than placebo[114–116]. However, many of these studies vary in their specific conclusions, likely due to inadequate sample sizes, weak study design, and the use of various probiotic strains making comparisons difficult[117]. In an effort to clarify which organisms were potentially effective in improving IBS symptoms, Ortiz-Lucas *et al*[118]specifically examined 10 randomized controlled trials. They found that probiotic combinations containing *Bifidobacterium breve, Bifidobacterium longum,* or *Lactobacillus acidophilus* improved pain

scores[118]. Meanwhile, probiotics containing *Bifidobacterium breve, Bifidobacterium longum, Lactobacillus casei, or Lactobacillus plantarum* improved distension scores[118].

Another therapeutic avenue for the treatment of IBS has included dietary changes. Fermentable carbohydrates can be difficult to absorb and have been shown to contribute to symptoms in IBS. Consistent with this finding, a low FODMAP (fermentable oligosaccharides, disaccharides, monosaccharides and polyols) diet has been shown to decrease symptoms in adults with IBS[119, 120]. Chumpitazi *et al*[121] confirmed that this response was also true in pediatric IBS. Additionally, they demonstrated that specific microbial signatures were associated with the efficacy of the FODMAP diet[121]. Specifically, FONDMAP responders had baseline microbiomes enriched with taxa with greater saccharolytic metabolic capacity and metabolic pathways related to carbohydrate metabolism[121].

Allergy and Asthma

The development of asthma and allergies has been associated with deviations in the developing microbiota. For example, infants colonized with *Escherichia coli* were at an increased risk of developing eczema, while infants colonized with *Clostridium difficile* were at increased risk of all atopic outcomes (eczema, recurrent wheeze, and allergic sensitization)[122]. Similarly, *Clostridium difficile* colonization at 1 month of age was associated with asthma at 6 to 7 years of age[123]. Antibiotic exposure in the first year of life has also been associated with an increased risk for the development of asthma in children, with this risk increasing in parallel with the number of courses of antibiotics prescribed[11].

These human findings have been further explored using mouse models of allergy and atopy. Allergic germ-free mice developed more severe disease than conventionally housed controls[124]. Importantly, this phenotype could be reversed by recolonization of the germ-free mice with conventional microbiota, demonstrating the important and influential role of the microbiota in allergic conditions[124]. Furthermore, in a mouse model of allergic airway inflammation (asthma), symptoms could be attenuated by exposure to *Lactobacillus reuteri*, but not *Lactobacillus salivarius*[125], signifying the importance of the bacterial species and strains that are present. In line with these findings, Russell *et al*[126] demonstrated that exposure to vancomycin, but not streptomycin, increased the severity of murine allergic asthma.

Obesity

Obesity has become a major global health problem, with increasing prevalence[127]. The patterns of maturation of microbial communities in infancy can affect the relative risk of becoming overweight and obese in later childhood. A recent longitudinal study of more than 900 infants found that mode of delivery and infant gut microbiota (specifically belonging to the *Lachnospiraceae* family) mediated the association between prepregnancy maternal overweight status and overweight status of children at 1 and 3 years of age[128]. Another study found that low levels of *Bifidobacterium* spp. and increased *Staphlococcus aureas* in infancy was associated with being overweight by age seven[12].

Further support for the microbiome's role in obesity was demonstrated by Cho *et al*[129]. In this study low dose antibiotic exposure in young mice led to increased adiposity, metabolic hormone levels, and SCFA levels, as well as changes to the hepatic metabolism of lipids and cholesterol[129]. Additional work by Cox *et al*[130] found that low dose penicillin given at birth can induce sustained effects on body composition and enhance high fat diet-induced obesity in mice. Furthermore, the obese phenotype was transferable to germ-free mice by transfer of low-dose penicillin microbiome[130], implicating the microbiome as the driver of this phenotype as opposed to antibiotics.

Autism Spectrum Disorder

While the underlying etiology of autism or autism spectrum disorder is not well understood, the intestinal microbiota is proposed to play a role in the development of autism. Children with autism have dysbiotic fecal microbiota, with greater abundances of *Bacteroidetes* and lesser abundances of *Firmicutes* compared to controls[13]. Luna et al[131] compared the mucosal microbiome of autistic children with functional abdominal pain to neurotypical children with function abdominal pain, and found distinct microbial signatures in autistic children that correlate with cytokine quantities and tryptophan homeostasis.

Children with regressive (late-onset) autism have increased numbers of fecal clostridial species, as well as the presence of non-spore-forming anaerobes and microaerophilic bacteria, which were absent in control children[132]. Due to frequent parental reports of an antecedent antibiotic exposure followed by chronic diarrhea in regressive autism, Sandler *et al*[133] hypothesized that, in some children, antibiotic-induced disruption of the microbiome may facilitate colonization by autism-promoting bacterial species. They tested this hypothesis by treating 10 autistic children with minimally absorbed oral vancomycin, and found that 8 of 10 children had short-term improvement in autistic symptoms[133]. While the improvements were not long-lasting, this report indicates a potential role for the gut microbiota in the symptomatology of autism spectrum disorder and thus warrants further investigation.

Murine studies have also supported a role of the microbiome in autism. Buffington *et al*[134] demonstrated impaired social behavior in the offspring of dams fed a high-fat diet, which were mediated by changes in the offspring's microbiota. While these pups' microbiota were notable for a significant reduction in *Lactobacillus reuteri*, supplementation with this bacterium reversed the observed social deficits[134]. deTheije *et al*[135] found that in utero valproic acid exposure resulted in decreased social behavior scores and impacted the gut microbiota of mice, with specific changes in *Bacteroidetes* and *Firmicutes*, similar to human autism studies. Together these results establish that in murine models of autism, behavioral alterations have been associated with altered microbial colonization.

CONCLUSIONS

In this review, we summarized the current understanding of the development of the pediatric microbiome, the impact of the microbiome on the developing brain and brain function through the gut-brain axis, and the impact of dysbiosis on disease development. The intestinal microbiome is an important factor in human growth and development, and the

appropriate balance of microbes throughout life plays a crucial role in the both health and disease. As emerging technology allows us to understand more about the microbiome and its many important functions, we in turn begin to understand the disease processes that the microbes impact. With this deeper knowledge and understanding comes the hope of new therapeutic targets and avenues through which to treat these diseases and promote human health across life stages and ages.

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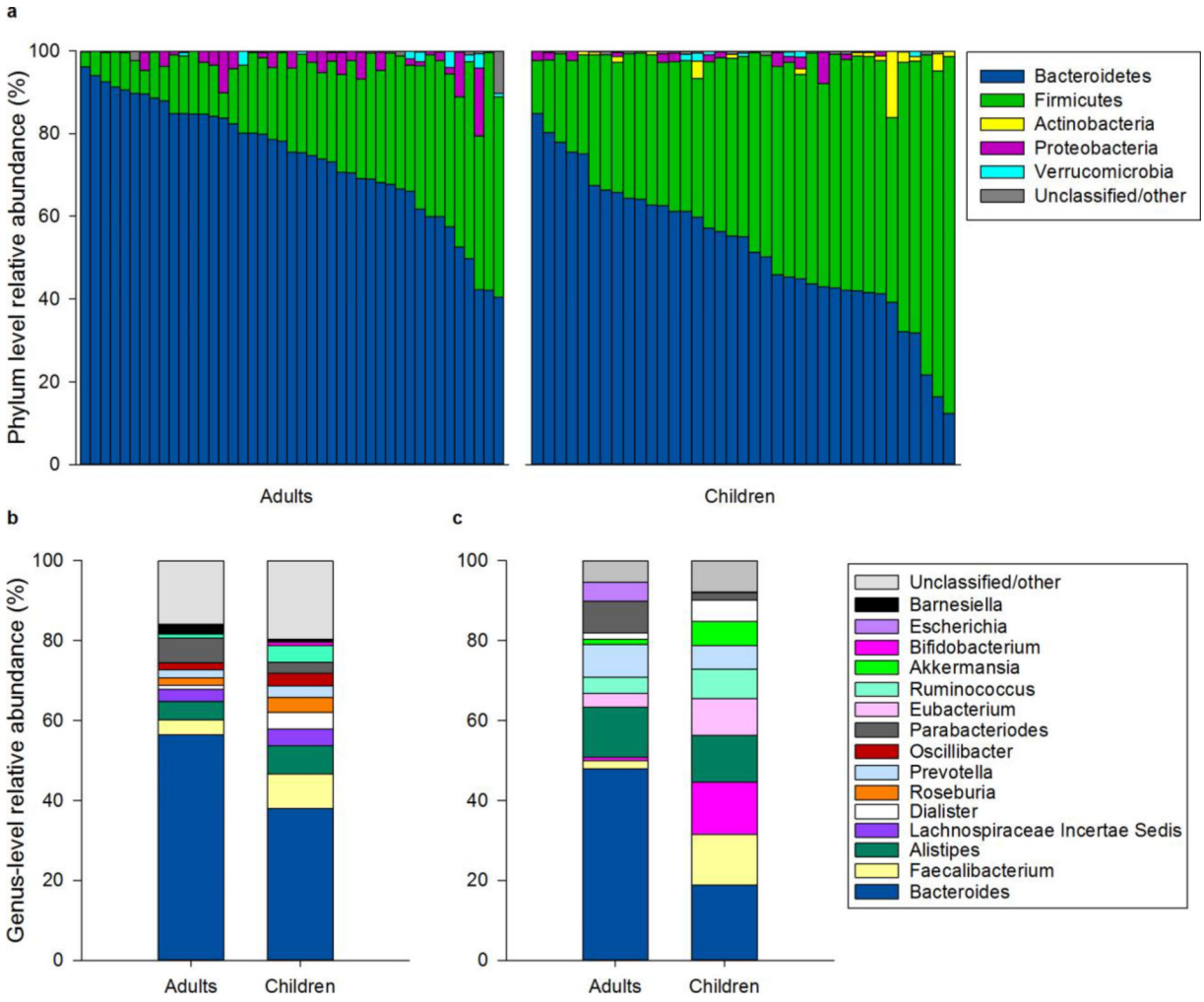

Figure 1.

Healthy pediatric and adult gastrointestinal tracts differ in relative abundances of gut bacterial taxa. (a) Phylum level relative abundances via 16S rRNA gene sequencing. Genus level relative abundances by (b) 16S sequencing and (c) shotgun metagenomic sequencing. (Adapted from Hollister et al.[47])

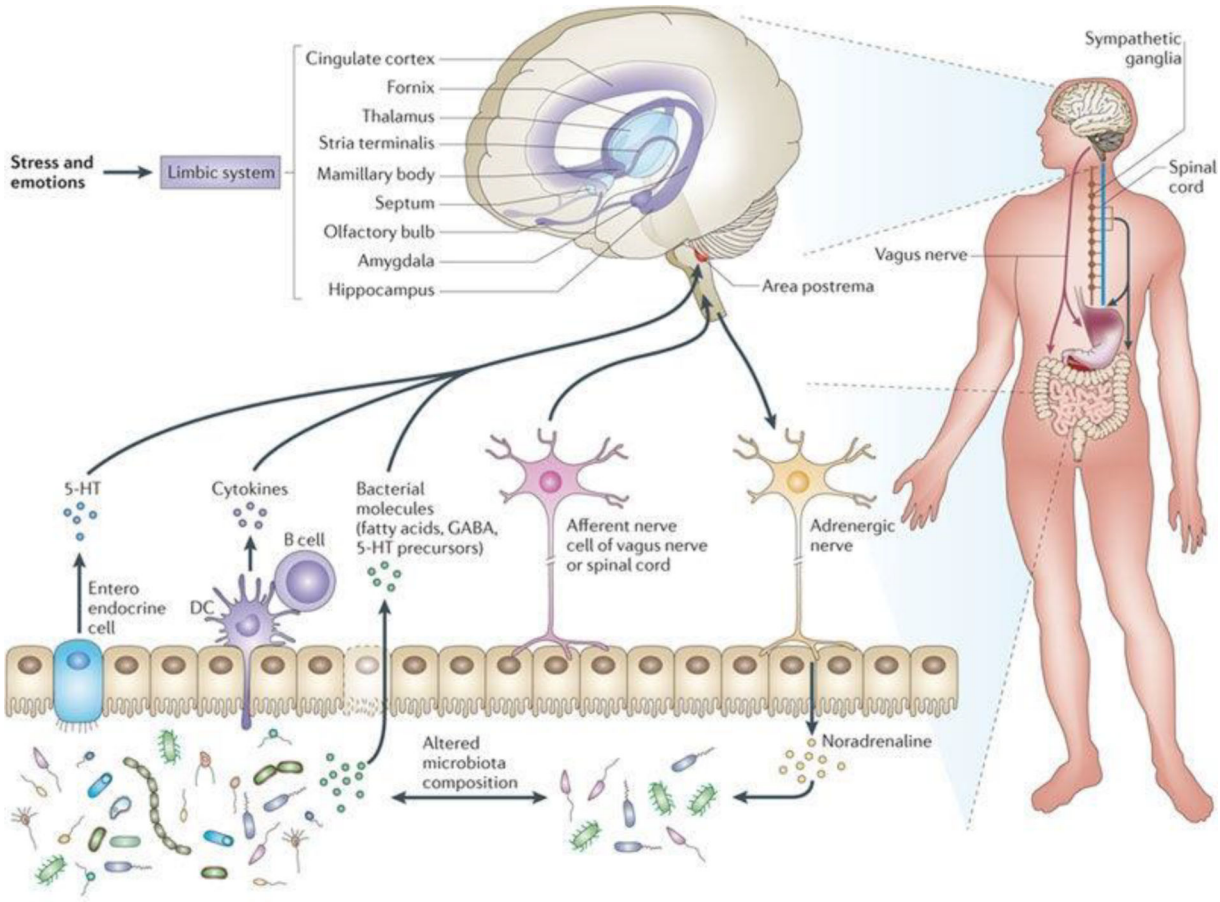

Figure 2.

The bidirectional gut-brain axis. The gut-brain axis is a complex interplay between the central nervous system, the neuroendocrine and neuroimmune systems, the autonomic nervous system, the enteric nervous system, and the microbiota. 5-HT, 5-hydroxytryptamine. DC, dendritic cell. GABA, γ-aminobutyric acid. (Adapted from Collins et al.[136])