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The microbiota–gut–brain axis: A promising avenue to foster healthy developmental outcomes

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Abstract

Fostering healthy developmental growth in the first years of life is associated with numerous favorable cognitive, social, and economic outcomes. Funding and promoting research aimed at identifying potential targets for early intervention should be a top priority for lawmakers and funders. One promising avenue of research and potential early intervention is the microbiota–gut–brain axis. In this report, we briefly examine the role of the gut microbiota in human life, focusing on links with health, cognition, and behavior. We then discuss the development of the gut microbiota and the critical early window in which colonization occurs. Then, we review current nonnutritive means of influencing the gut microbiota in early life. Finally, we discuss the implications this work has for early intervention in low-income communities and end with recommendations regarding further research and research funding priorities.

KEYWORDS

development, infancy, intervention, microbiota–gut–brain axis, socioeconomic status

1 | INTRODUCTION

Targeted early intervention into controllable factors such as parenting quality, access to quality education, health care, and adequate nutrition in the first years of life is associated with lifelong beneficial outcomes (e.g., Muennig et al., 2009; Campbell et al., 2012). These benefits, which outweigh the costs of initial intervention, can be seen at individual (e.g., greater social competence, more earnings, higher educational attainment) and societal levels (e.g., decreased rates of delinquency/crime; higher tax revenues; Karoly, Kilburn, & Cannon, 2005). Moreover, early investment is often cost-effective and associated with larger benefits than later remediation (Carneiro & Heckman, 2003). Given this, funding and promoting research aimed at identifying potential targets for early intervention, particularly in communities at risk for unfavorable outcomes, should be a top priority for lawmakers and funders.

One burgeoning line of work that may have a place in early intervention is that concerning the microbiota–gut–brain axis. In this manuscript, we begin by briefly examining the role of the gut microbiota in human life, focusing on links with health, cognition, and behavior. Following this, we discuss the development of the gut microbiota and the critical early window in which colonization occurs. Then, we review current nonnutritive means of influencing the gut microbiota in early life. Finally, we discuss the implications this work has for early intervention in low-income communities and end with recommendations regarding further research and research funding priorities.

2 | THE MICROBIOTA–GUT–BRAIN AXIS

The human gut contains more than 10 trillion microbes, comprised largely of bacteria but also including archaea, fungi, yeasts, and protozoa. These microscopic microbes, collectively known as the gut microbiota, are so numerous that they weigh approximately the same as a human brain (Dinan et al., 2015). The gut microbiota operates as a metabolic organ, taking on functions not encoded in the human genome such as generating metabolites not produced by the

human body (Gonzalez et al., 2011) and providing essential nutrients from some polysaccharides and carbohydrates that are otherwise indigestible (Adlerberth & Wold, 2009; Diaz Heijtz, 2016). Further, the gut microbiota is implicated in the development, maturation, and maintenance of many essential systems in human health, such as the immune system (de Weerth, 2017), gastrointestinal tract (Diaz Heijtz, 2016), and metabolism (Nicholson et al., 2012; Tremaroli & Bäckhed, 2012).

Current research also indicates a role for the gut microbiota in the development of the brain and finds evidence for bidirectional communication between the two (e.g., Fung, Olson, & Hsiao, 2017). The enteric nervous system, a system of neurons embedded in the lining of the gastrointestinal system, relies on neural, endocrine, immune, and humoral pathways to enable gut–brain communication (Carabotti, Scirocco, Maselli, & Severi, 2015). Moreover, intestinal bacteria can produce neurotransmitters such as serotonin that have the potential to affect the brain, human behavior, emotions, and potentially even higher order cognition such as decision-making and planning (Cryan & Dinan, 2012; Strandwitz, 2018). The close communication between the gut and the brain, as well as the microbiota–gut–brain axis' role in fostering the development of vital human systems, illustrates the key role this axis plays in development and health.

2.1 | The microbiota and health

Research is rapidly uncovering links between the gut microbiota and human health and disease. Much of the knowledge underlying this research comes from experimental animal models capable of demonstrating causal links between microbial manipulations and specific physiological or behavioral outcomes. For example, some studies use germ-free rodents raised in sterile environments to determine how living without a microbiota affects development. Others use antibiotics to induce intestinal microbial imbalances in typically developing animals, or probiotics, defined as "live microorganisms which, when administered in adequate amounts, confer a health benefit on the host" (Food & Agriculture Organization of the United Nations/World Health Organization, 2002), to examine the effects of promoting gut health. In humans, experimental methods to examine the links between the gut microbiota and health are generally limited to randomized controlled trials involving probiotics or treatments for ill individuals. More commonly, scientists use cross-sectional studies in which the microbiota of two or more groups of interest are compared.

A healthy gut microbiota is one that evinces diverse colonization in which microorganisms with positive effects on health are more numerous than ones that may be harmful and in which the enteric cells of the intestinal wall effectively contain these bacteria, preventing them from entering the bloodstream. Contrarily, dysbiosis refers to a microbial imbalance in which harmful bacteria disproportionately colonize the gut in response to host-mediated inflammation. This inflammation typically results from infection, a genetic predisposition, or a chemical trigger of some sort (e.g., Lupp et al., 2007; Rawls, 2007). Studies in animals and adult humans suggest that a healthy gut microbiota is implicated in many physiological, metabolic, and immune-related processes (for reviews see, Haase et al., 2018; Pascale et al., 2018; Rowland et al., 2017), whereas dysbiosis is associated with metabolic, inflammation-related, pancreatic, and intestinal diseases such as obesity, cancer, and cardiovascular disease (for reviews see, Akshintala, Talukdar, Singh, & Goggins, 2018; Castaner et al., 2018; Feng, Chen, & Wang, 2018; Lazar et al., 2018; Pascale et al., 2018; Wang & Zhao, 2018).

The microbial influence on health begins early in life. For example, early gut microbiota alterations in mice (induced by an antibiotic) can have long-term consequences on adult metabolic functioning and adiposity (Cox et al., 2014). In humans, associations between early microbiota composition and child health are well documented and growing. Studies examining the correlates of antibiotic use, probiotic use, and microbiota composition suggest that imbalances in the gut microbiota in infancy and childhood are implicated in: increased risk for child obesity (e.g., Dogra et al., 2015; Kozyrskyj, Kalu, Koleva, & Bridgman, 2016), irritable bowel syndrome (e.g., Saulnier et al., 2011), allergies (e.g., Noverr & Huffnagle, 2005), atopic disorders (Penders et al., 2007), and asthma (e.g., Kummeling et al., 2007). Research continues to emerge illustrating the gut microbiota's importance in establishing and maintaining physical health beginning in the earliest days of life.

2.2 | The microbiota, cognition, and behavior

The microbiota–gut–brain axis is likely also involved in a wide variety of cognitive processes in living creatures. In animal studies, the gut microbiota is implicated in learning, stress, addiction, and some social behaviors (for reviews see Cussotto et al., 2018; Münger, Montiel-Castro, Langhans, & Pacheco-López, 2018). Studies with adult humans demonstrate a tentative link between the gut microbiota and mood disorders (see Liu & Zhu, 2018), but the findings regarding this and other forms of cognition are less consistent, particularly in studies using probiotics (see Sarkar et al., 2018). The gut microbiota may also be implicated in some neuroimmune diseases, including Parkinson's and Alzheimer's diseases, schizophrenia, multiple sclerosis, and autism spectrum disorders (see Lombardi et al., 2018).

It is surprising that few studies have yet examined relations between microbiota composition and cognition in infants and young children, as this is when potential effects may be largest (de Weerth, 2017). In the few studies examining the association between probiotics or prebiotics (defined as "a substrate that is selectively utilized by host microorganisms conferring a health benefit"; Gibson et al., 2017) and cognition in healthy infants and children, the findings are mixed. Some studies find no difference in neurodevelopmental outcomes between infants who have and have not ingested probiotics, despite the presence of physical health benefits (e.g., Akar et al., 2016; Sari et al., 2012), whereas others have found improved social and school functioning in young children who ingest them (e.g., Ringel-Kulka, Kotch, Jensen, Savage, & Weber, 2015). Studies

examining gut microbial composition and behavior have found that early microbial composition is linked with colic in very young infants (de Weerth, Fuentes, & de Vos, 2013; de Weerth, Fuentes, Puylaert, & de Vos, 2013; Rhoads et al., 2018) and aspects of temperament, visual reception, and language acquisition in toddlers (Carlson et al., 2018; Christian et al., 2015).

2.3 | Mechanisms underlying gut–brain associations

The mechanisms accounting for the gut microbiota's links with physical and mental health have yet to be fully elucidated but are likely complex and overlapping. For instance, researchers have proposed that some of the metabolites produced by the microbiota (e.g., short-chain fatty acids; Chambers, Preston, Frost, & Morrison, 2018), serve a communicatory role within the central nervous system. They can induce important physiological changes capable of affecting immune functioning and health. Studies with animals also demonstrate that microbial alterations can induce several neurochemical changes (e.g., altered brain-derived neurotrophic factor levels in the hippocampus and cortex; reduced synaptic plasticity gene expression; Diaz Heijtz et al., 2011; Neufeld et al., 2010; Sudo et al., 2004) capable of affecting the brain and behavior. For detailed reviews of these and other mechanisms, see Bruce-Keller, Salbaum, and Berthoud (2018) and Martin, Osadchiy, Kalani, and Mayer (2018). This preliminary work suggests that the microbiota–gut–brain axis plays a complex part in human functioning and that a healthy microbiota may be an essential component of optimal development.

2.4 | The development of the gut microbiota

The development of the human microbiota likely begins prenatally. The intrauterine environment hosts both gram-positive and gram-negative bacteria in a moderate percentage of mothers at time of delivery (Stout et al., 2013), and microbes have been identified in the placenta (Aagaard et al., 2014). Infants are nonetheless born with nearly sterile intestines with a very low and nondiverse bacterial load in the meconium (de Weerth, Fuentes, Puylaert, et al., 2013). Intestinal population by bacteria largely occurs during delivery or shortly thereafter as the infant gut is colonized with dozens of bacterial species in the first days of life.

Over the next few years, the diversity of these bacterial species and their associated functions increase rapidly, slowing in early childhood (see Lynch & Pedersen, 2016, for a review; Cheng et al., 2016; Yatsunenko et al., 2012) but continuing into adulthood. The number of bacterial taxonomic groups and functional genes in the microbiota is like those of adults by preadolescence, but even then, the functionality of the microbiome differs and is more focused on developmental processes (such as vitamin synthesis) than processes of aging (such as controlling inflammation and obesity; Hollister et al., 2015). Among healthy children and adults, evidence indicates only 35%–45% taxonomic similarity in microbiota composition but 90%–96% similarity in functionality, indicating that microbiota-related health lies not only in the composition of the microbiota, but also in its diversity and functions in development (Hollister et al., 2015; Human Microbiome Project Consortium, 2012).

Considering that the human brain is also developing in the first years of life, it is reasonable to hypothesize that gut microbial influences on the brain may be largest in early development (de Weerth, 2017). Animal models provide support for this notion, finding that the early gut microbiota plays a pivotal role in synaptogenesis and the myelination of brain areas associated with motor control and cognitive functioning (Diaz Heijtz, 2016; Hoban et al., 2016). Moreover, the gut microbiota is associated with microglia maturation and function, both of which are critical in the development of the immune system (Erny et al., 2015). Research in humans provides preliminary support as well, finding that late bacterial acquisition and low bacterial diversity in the microbiota are associated with delayed maturation of the immune system in the first 2 years of life (Jakobsson et al., 2014). In addition, many of the metabolic functions (e.g., metabolism of nutrients and energy transfer from the diet; Diaz Heijtz, 2016) of the intestinal microbiota are implicated in healthy brain development processes that occur during early sensitive or critical periods.

For this reason, fostering early, diverse, and balanced microbial colonization of the gut is vital for establishing the bacterial community needed to set children on a healthy developmental trajectory early in life. Research indicates that breastfeeding may play a critical role in this, providing the infant gut with both bacteria and human milk oligosaccharides (HMOs; Martín et al., 2012). HMOs are a diverse set of glycans that, although indigestible to humans, promote the growth of healthy strains of bacteria in the infant gut (Bode, 2012). Exclusive breastfeeding in the first 6 months of life protects the microbiota, increasing its resistance to external influences in infancy (Carvalho-Ramos, Duarte, Brandt, Martinez, & Taddei, 2018). Other research on microbial manipulation focuses on the promise of dietary intervention using probiotics and prebiotics, presented elsewhere in this special issue. However, a multitude of factors beyond diet are implicated in early colonization, including the health of the maternal microbiota, type of delivery, environmental sanitary conditions, antibiotic use, and even the presence of siblings or pets (Adlerberth & Wold, 2009; Koenig et al., 2011; Song et al., 2013). In the following section, we discuss nonnutritive means to potentially influence the gut microbiota in infancy.

3 | INFLUENCING THE GUT MICROBIOTA IN EARLY DEVELOPMENT

3.1 | Managing the maternal microbiota

Evidence suggests that the human body prepares itself for delivery by altering the prevalence of certain bacterial phylotypes in the maternal microbiota of various body sites (e.g., the gut, vagina, oral cavity, placenta; Nuriel-Ohayon, Neuman, & Koren, 2016). However, environmental influences can still affect the composition and diversity of the maternal microbiota, and this can have consequences on the pregnancy and child outcomes (Dunlop et al., 2015). Two

particularly important influences on the maternal microbiota and potentially the infant microbiota during pregnancy are maternal use of antibiotics and maternal stress.

3.1.1 | Antibiotics

Unnecessary antibiotics during pregnancy may be a barrier to optimal infant gut colonization. Several studies note an association between prenatal antibiotic use and reduced abundance of healthy bacteria in offspring at birth (e.g., Mshvildadze et al., 2010; Keski-Nisula et al., 2013). One study cites an 84% increased risk of developing childhood obesity in children whose mothers received any type of antibiotic prenatally (Mueller et al., 2015). Currently, many pregnant women are prescribed antibiotics known to cross the placenta (Langdon et al., 2016). These antibiotics can be lifesaving and medically necessary. However, until their full effects on the infant microbiota can be explored, judicious and limited antibiotic use is warranted during pregnancy and labor.

3.1.2 | Stress

In addition, regulating maternal stress during pregnancy may prove to be an important step in promoting healthy colonization of the unborn child's gut microbiota (de Weerth, 2017, 2018). Evidence indicates that both self-reported and physiologically measured prenatal maternal stress may influence the infant microbiota. One study found that infants of stressed mothers had a microbiota profile characteristic of increased inflammation, and more mother-reported infant gastrointestinal problems and allergic reactions (Zijlmans, Korpela, Riksen-Walraven, de Vos, & de Weerth, 2015). Although preliminary, this and other animal studies (e.g., Bailey, Lubach, & Coe, 2004) demonstrate that maternal prenatal stress may have a lasting and negative effect on the infant microbiota. While it is not always possible to manage maternal stress, programs aimed at its reduction (e.g., stress-reducing interventions and parenting programs; paid maternal leave and access to health care) may be an important step in promoting healthy infant microbiota development. In addition, prenatal screening for maternal stress may help identify mothers who need additional support during pregnancy.

3.2 | Cesarean delivery (C-section)

Mode of delivery has a direct impact on microbial composition and diversity (e.g., Biasucci et al, 2010; Dominguez-Bello et al., 2010). Studies show that children born via vaginal delivery have gut microbiota resembling the fecal and vaginal flora of their mother, whereas children born via C-section have gut microbiota resembling the mother's skin or oral flora or the birth environment (e.g., Bäckhed et al., 2015). In addition, C-sections potentially delay crucial mother infant skin-to-skin contact and the initiation of breastfeeding (Prior et al., 2012), two important contributors to early microbial development. Many C-sections also include giving the mother powerful antibiotics (either before or during the operation; Smaill & Grivell, 2014) to avoid postoperative infection. Antibiotics administered before the umbilical cord is clamped are potentially transferred to the fetus; their effect on the newly developing microbiota is unknown (Smaill & Grivell, 2014). The combined effect of these factors presents a substantial risk for the healthy colonization and development of the infant microbiota. In fact, differences in gut microbial colonization and microbiota diversity that are associated with mode of delivery have been reported at 6 months (Rutayisire, Huang, Liu, & Tao, 2016), 2 years (Jakobsson et al., 2014), and even in adulthood (Goedert, Hua, Yu, & Shi, 2014), although another study found no differences (Chu et al., 2017).

Early microbial differences may have long-term impacts on individual health. C-section is linked with a host of later developing diseases, many of which are also associated with a disrupted microbiota. For example, one retrospective study in more than 2 million Danish children found increased rates of asthma, juvenile arthritis, systematic connective tissue disorders, inflammatory bowel disease, immune deficiencies, and leukemia among children born via C-section (Sevelsted, Stokholm, Bønnelykke, & Bisgaard, 2015). Other studies confirm that C-section is associated with increased risk for diseases linked with microbial alterations, such as obesity (e.g., Li, Zhou, & Liu, 2013), gastroenteritis, asthma, and autoimmune disease later in life (e.g., Kristensen & Henriksen, 2016). Importantly, these outcomes may also be associated with the medical indications for having a C-section (e.g., abnormal labor). However, given the link of these diseases with microbial alterations, investigating the role of the microbiota in their development is warranted too.

The World Health Organization currently recommends C-section only be performed in cases where it is medically necessary (Betran, Torloni, Zhang, & Gülmezoglu, 2015). Medical providers can increase chances of vaginal birth by following evidence-based guidelines that take into account typical labor progression and fetal heart monitoring during birth (Spong, Berghella, Wenstrom, Mercer, & Saade, 2012). In addition, studies should continue to examine care options that increase chances of acquiring a healthy gut microbiota in infants born via C-section (e.g., Smith, Plaat, & Fisk, 2008).

3.3 | Vaginal seeding

Vaginal seeding, a controversial procedure that may offer a way to influence the microbiota of infants born by C-section, is the process of inoculating a sterile cotton gauze or swab with the mother's vaginal fluids prior to delivery and transferring her vaginal bacteria to her neonate by swabbing his or her mouth, nose, and skin with it. The only study to date on vaginal seeding found that four cesarean-born infants who underwent vaginal seeding had oral, skin, and anal microbiota that more closely resembled those of vaginally born infants than cesarean-born infants for one month postbirth (Dominguez-Bello, et al., 2016). Despite a lack of research, vaginal seeding has gained traction in the scientific community and media. This has led some authors to call for caution due to the very real risk of spreading unknown maternal infections to vulnerable infants,

particularly since the link between C-section and later illness is likely the result of multiple factors and not simply lack of contact with the maternal microbiota (e.g., Cunnington et al., 2016; Stinson, Payne, & Keelan, 2018). The American College of Obstetricians and Gynecologists currently recommends that vaginal seeding only be performed in the context of institutional review board-approved research (ACOG, 2017).

3.4 | Delivery and postbirth practices

Doctors and nurses involved in pre- and postnatal care have the potential to influence the colonization of the infant microbiota through the care decisions they make. Although controversial, there is some evidence that certain common procedures, such as frequent cervical exams, urinary catheterization, and electronic fetal monitoring, while not associated with the microbiota directly, can increase risk for infections that result in antibiotic use or cesarean birth (Jansen, Gibson, Bowles, & Leach, 2013). Care providers present at the time of birth can encourage mothers to make early skin-to-skin contact if appropriate and to initiate breastfeeding if the mother plans to do so. Finally, the use of preventive antibiotic treatment in the neonate may affect normal microbial colonization (see Neuman, Forsythe, Uzan, Avni, & Koren, 2018 for a review). Although more prospective multicentered research is warranted before modifying care protocols, a recent study found that the use of antibiotics in neonates with suspected early-onset sepsis can be reduced by 44% through a change in medical practices (Achten, Dorigo-Zetsma, van der Linden, van Brakel, & Plötz, 2018).

3.5 | Fecal transplant

Although fecal transplant is currently only employed to treat life-threatening recurrent *Clostridium difficile* infection in adult populations, mentioning it here is warranted as it may one day prove to be a valuable technique for positively manipulating the gut microbiota in early life as well. Fecal microbial transplantation involves transferring the stool (or its cryopreserved microbial components) of a healthy donor to an individual with a dysbiotic or pathogenic gut microbiota. This is traditionally accomplished via a nasogastric or nasoenteric tube, an enema, or is done during an endoscopy. Recently, researchers have also developed acid resistant oral capsules containing the donor's cryopreserved microbes (Patel & Spector, 2016; Youngster et al., 2014; and see Bouri & Hart, 2018, for a review of current best practices). Studies have also begun to examine whether fecal transplant can be used to treat irritable bowel syndrome, ulcerative colitis, Crohn's disease, and the gastrointestinal and social symptoms in autism (Holleran et al., 2018; Kang et al., 2017). Evidence suggests that the risks associated with fecal transplant are low (Baxter & Colville, 2016; Meyers, Shih, Neher, & Safranek, 2018), even in immunocompromised and elderly populations (Agrawal et al., 2016; Kelly et al., 2014). However, more research is needed to ascertain the full scope of risks associated with the procedure.

4 | IMPLICATIONS FOR LOW-INCOME COMMUNITIES

The literature just reviewed holds promise for all human populations, but for some, may represent a critical step in improving health outcomes. One vulnerable population that may benefit from continued research into the microbiota–gut–brain axis is the socioeconomically disadvantaged. Low socioeconomic status (SES) is associated with multiple risk factors linked with later mental and physical illness, such as early life stress, adverse childhood experiences (e.g., Cambois & Jusot, 2011; Chapman et al., 2004; Dong et al., 2004), reduced access to healthcare (Anderson & Armstead, 1995), increased engagement in unhealthy behaviors like smoking and alcohol dependency (Bloomfield et al., 2006; Marmot, 2006), and decreased engagement in positive health behaviors like healthy eating and exercise (Brug, 2008; Gidlow, Johnston, Crone, Ellis, & James, 2006). Low-SES status across the globe is associated with higher rates of morbidity and mortality (e.g., Signorello et al., 2014) and higher incidence of some of the diseases previously mentioned in this review, such as asthma (Shankardass et al., 2011) and diabetes (Krishnan, Cozier, Rosenberg, & Palmer, 2010). Moreover, low SES is also associated with lower cognitive abilities in middle childhood (Lawlor et al., 2006) and adulthood (Kobrosly et al., 2011).

It is unclear whether these disparities in mental and physical health are at least in part a direct (or indirect) result of differences in gut microbiota composition, but there are reasons to hypothesize that they may be (Rook, Raison, & Lowry, 2014). Many characteristics associated with low-SES neighborhoods and lifestyles (e.g., processed foods, sedentary lifestyle, psychosocial stress, exposure to pollutants and endocrine disrupters) are also associated with reduced gut microbial diversity (Conlon & Bird, 2014; Diez Roux & Mair, 2010). Studies also show that low-income women are less likely to breastfeed than women from high-SES backgrounds (in high-income countries; e.g., Heck, Braveman, Cubbin, Chávez, & Kiely, 2006; Ruijsbroek et al., 2011), even when they express the intention to do so in pregnancy (Conner et al., 2013). Only two studies so far have examined differences in microbial composition between high- and low-SES populations. In one, higher SES was associated with greater alpha-diversity and population rates of particular microbes in the colonic microbiota (Miller et al., 2016). In the other, distinct differences in microbial composition were found between the gut microbiota of low-income Bangladeshi children and upper- to middle-class American children of the same age (Lin et al., 2013). In both cases, the effects of these differences on health are unknown. However, given the importance of the gut microbiota in health and its role in brain development, low-cost interventions aimed at positively altering microbial composition in early life may be especially promising for disadvantaged communities. Importantly, although SES is a common measure of disadvantage, these benefits could also be promising for higher SES communities in other disadvantaged (e.g., war-torn; high stress) contexts.

5 | FUTURE DIRECTIONS AND RECOMMENDATIONS IN MICROBIOTA RESEARCH

Although the body of literature just reviewed speaks to the promise this line of work holds for influencing healthy development early in life, substantial gaps in knowledge still exist. Supporting research into the microbiota–gut–brain axis should be a top concern for funding agencies and policy makers interested in identifying potential targets for affordable early intervention. Funding should be prioritized toward three types of research that are likely to generate new knowledge that can be applied to programs promoting physical and mental health in humans: basic, intervention, and longitudinal research.

5.1 | Basic research and the promise of omics technologies

It is largely thanks to the recent metagenomic revolution that we can explore and characterize the composition of the gut microbiome (i.e., the complete set of genes associated with the microbiota), its basic functions, and its links with health and disease. Researchers should continue to expand on this burgeoning knowledge with cross-disciplinary investigations to build a complete picture of the complex functionality of the microbiota. Researchers in the fields of genomics (e.g., Feero & Guttmacher, 2014), metabolomics (e.g., Patti et al., 2012), culturomics (e.g., Lagier et al., 2018), proteomics (e.g., Ruiz et al., 2016), and transcriptomics (e.g., Castro-Nallar et al., 2015) should employ a multiomic approach to cataloguing the incredible variety of microbes in the human microbiota, their metabolic functions, their relative activity in the gut, and their communication and interactions with each other and the brain. Such cross-collaboration will allow scientists to zero in on microbial profiles associated with favorable and maladaptive outcomes. As mentioned, even healthy adults do not have one specific gut microbial composition, so understanding the wide variety of profiles or specific microbes that can confer health benefits or risks will be an important step in identifying and treating at-risk or disordered gut microbial communities.

5.2 | Intervention research

In addition, funding should be allocated for researchers interested in creating and studying affordable interventions designed to influence gut health. When possible, RCTs will move the field from correlational to causational research. Top priority should be given to studies that attempt to combine basic science and intervention research, as these are the studies that will begin to identify the mechanisms behind structural and functional changes in the microbiome and their influences on health, behavior, and cognition.

Interventions using probiotics are certainly relevant to this endeavor, as probiotics are an increasingly affordable (e.g., Reid et al., 2018) and low-risk (e.g., van den Nieuwboer et al., 2015; van den Nieuwboer, Claassen, Morelli, Guarner, & Brummer, 2014) means of influencing gut health (e.g., George Kerry et al., 2018). Similarly, interventions using prebiotics will yield valuable insights into bacterial proliferation and microbial maintenance. Other potentially low-cost interventions aimed at improving gut health might include components designed to: increase exclusive breastfeeding in the first months of life, reduce maternal prenatal stress, and increase the chance of vaginal delivery. In addition, interventions designed to affect other facets of health may benefit from including the gut microbiota as an additional variable of interest. It may be that other lifestyle factors (e.g., psychosocial support, participation in psychotherapy, the use of alcohol or other recreational drugs) have undiscovered influences on gut health.

5.3 | Longitudinal work

Finally, research examining the development of the microbiota longitudinally can help elucidate when and how profiles shift and what additional factors beyond those discussed here might influence their evolution. Such investigations may clarify whether sensitive or critical periods exist for developing, maintaining, and treating gut health in humans. Of particular interest to funders might be investigations intending to combine all three types of research mentioned here. Longitudinal investigations meant to track gut microbial changes in response to intervention, and how those changes influence health, cognition, and behavior, represent a critical step in uncovering ways in which the microbiota–gut–brain axis can be used as a tool to set humans on a healthy developmental trajectory early in life.

6 | SUMMARY

The preceding sections present a substantial body of literature describing the gut microbiota's potential role in human health, cognition, and behavior. Following this, and the potential role of the gut microbiota in brain development, we presented the case that the earliest days of life may represent a particularly critical time for intervening in gut health to ensure healthy developmental outcomes. Attempts to positively influence the gut microbiota are in their infancy as we discover new targets of intervention and methods of manipulation. Continued investigations into the basic science behind the microbiota–gut–brain axis and the potential benefits of its role in early intervention may prove to be a key step in achieving the United Nation's Sustainable Development Goal for people to "ensure that all human beings can fulfill their potential in dignity and equality (UN General Assembly, 2015)." Such a goal benefits not only the recipients of such intervention, but the societies they live in as well.

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