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Review article

Diet-induced dysbiosis of the maternal gut microbiome in early life programming of neurodevelopmental disorders

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ABSTRACT

The maternal gut microbiome plays a critical role in fetal and early postnatal development, shaping fundamental processes including immune maturation and brain development, among others. Consequently, it also contributes to fetal programming of health and disease. Over the last decade, epidemiological studies and work in preclinical animal models have begun to uncover a link between dysbiosis of the maternal gut microbiome and neurodevelopmental disorders in offspring. Neurodevelopmental disorders are caused by both genetic and environmental factors, and their interactions; however, clinical heterogeneity, phenotypic variability, and comorbidities make identification of underlying mechanisms difficult. Among environmental factors, exposure to maternal obesity *in utero* confers a significant increase in risk for neurodevelopmental disorders. Obesogenic diets in humans, non-human primates, and rodents induce functional modifications in maternal gut microbiome composition, which animal studies suggest are causally related to adverse mental health outcomes in offspring. Here, we review evidence linking maternal diet-induced gut dysbiosis to neurodevelopmental disorders and discuss how it could affect pre- and early postnatal brain development. We are hopeful that this burgeoning field of research will revolutionize antenatal care by leading to accessible prophylactic strategies, such as prenatal probiotics, to improve mental health outcomes in children affected by maternal diet-induced obesity.

Contents

1. Introduction

Neurodevelopmental disorders are classified as a group of neurological conditions with onset in early development characterized by deficits ranging from specific limitations in learning, speech, or motor skills, to more general impairment of social skills and intellectual ability (Battle, 2013; Muhle et al., 2018). The etiology of neurodevelopmental disorders is multifactorial–that is, determined by the interaction of genetic, epigenetic, and/or environmental factors. This complex and diversified etiology is reflected in the clinical heterogeneity and phenotypic variability observed between patients and has made identification of mechanisms con-

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tributing to their onset difficult (Muhle et al., 2018). Yet, given the growing prevalence of neurodevelopmental disorders (Zablotsky et al., 2019), it is critical to identify modifiable risk factors to decrease disease prevalence and reduce associated personal and societal costs.

To date, a great number of studies have focused on the genetic basis of neurodevelopmental disorders, autism spectrum disorder (ASD) in particular (de la Torre-Ubieta et al., 2016). An important turning point in the investigation of the genetics of ASD occurred in 2005 with the introduction of new techniques which allowed for extensive sequencing of genomes of affected individuals. In contrast with candidate gene studies, genome wide association studies (GWAS) facilitate hypothesis-free methods for the identification of associations between loci and traits (Tam et al., 2019), resulting in an unbiased, large-scale approach for the investigation of complex traits, such as those that manifest in ASD patients.

The findings of genomic and epigenomic studies highlight the incredible complexity of genetic alterations associated with neurodevelopmental disorders (Parenti et al., 2020). However, genetics fails to completely account for the incidence of neurodevelopmental disorders (Hallmayer et al., 2011), thus implicating environmental factors in the onset and pathological manifestation of these disorders. Moreover, while a genetic insult may be the initiating factor for disease that may or may not manifest phenotypically, a fetal environmental insult could tip the balance toward or exacerbate phenotype manifestation in an individual genetically predisposed. Thus, an innovative and relatively tractable approach to reducing symptom burden on patients and their families would be to prophylactically address modifiable environmental risk factors of disease, even if they are not the initiating cause.

The term “environmental factors” encompasses a myriad of exposures, and the sum of all environmental factors encountered by individuals throughout the course of life, from conception onward, has been coined the “exposome” (Wild, 2012). The early-life exposome is primarily determined by factors that affect the maternal environment which in turn affect the developing fetus/infant (Jansson and Powell, 2007). Brain development is particularly vulnerable to the influence of the exposome, given that it is an exquisitely orchestrated process involving several critical processes that necessarily occur at specific developmental time points. Consequently, neurodevelopmental disorders have been reported to be caused by the disruption of many stages of brain formation, spanning from cell proliferation to neuronal migration, neurite outgrowth, spine and synapse formation, among many others (Bourgeron, 2015).

Exposure to harmful environmental factors during developmental critical periods can exert a profound impact on long-term mental health outcomes, consistent with the concept of the ‘developmental origins of health and disease (DOHaD)’ (Gluckman et al., 2016). DOHaD, or the “Barker hypothesis,” postulates that adverse events during gestation/early postnatal life are responsible for fetal programming of the structure and function of cells, tissues, and organs, leading to permanent alterations in the individual’s physiology that then predispose the individual to a plethora of health conditions, including behavioral and cognitive disorders.

Given the impact of maternal nutrition on fetal and early postnatal development (Jasarevic and Bale, 2019) and the global prevalence of maternal overweight and obesity (Branum et al., 2016; Davis, 2020; Deputy et al., 2018), in this review, we focus on the effects of maternal diet-induced obesity on prenatal and early postnatal offspring brain development and its lasting consequences on brain function and behavior. We specifically consider the connection between diet-induced dysbiosis of the maternal gut microbiome, its effect on fetal and early postnatal brain development in health and disease, as well as the therapeutic opportunity presented by targeting the maternal gut microbiome to prophylactically prevent the neuropathology underlying some cases of neurodevelopmental disorders. Furthermore, we make the case that the rising prevalence of obesity among women of child-bearing age is a mental health crisis exacerbated by social determinants of health. Finally, we propose that a prenatal probiotic regimen, analogous to the success of government-mandated folic acid supplementation in reducing the incidence of neural tube defects (NTDs) (MRC Vitamin Study Research Group, 1991; Czeizel and Dudas, 1992), may stem the tide.

2. The maternal exposome in neurodevelopmental pathology

Neurodevelopmental disorders are characterized by developmental deficits which are responsible for impairments of social, personal, and/or occupational functioning (Battle, 2013). Among neurodevelopmental disorders, the prevalence of ASD has increased dramatically in recent decades (Zablotsky et al., 2019). Clinical manifestation of ASD differs based on the severity of the disorder, developmental stage, and age of the subjects. The term “spectrum” is used to include a broad range of disorders previously identified as high-functioning autism, pervasive developmental disorders not otherwise specified, atypical autism, and others. The core features of ASD (communication deficits, social deficits, and stereotypic behavior) often appear in early development, but the specific age at which a diagnosis is made may vary in relation to the subjects and their environment, particularly between sociodemographic populations. In most cases, ASD is not diagnosed until after age three; however, a recent study among African American children with autism suggests that diagnosis is even further delayed in this population, with individuals averaging over five years of age at time of diagnosis (Constantino et al., 2020). Given that early detection and intervention are associated with better patient outcomes (Elder et al., 2017), it is critical to address the gap in early diagnosis rates and reduce barriers to access for therapy for all children, regardless of socioeconomic status. With some exceptions, ASD symptoms usually improve during adolescence; however, only a portion of affected individuals can work and live independently in adult life, depending on the severity of the disorder.

Despite its multifactorial etiology, ASD aggregates in families; consequently, ASD has classically been considered solely as a genetic disorder (Sandin et al., 2017). However, a broad review (Ronald and Hoekstra, 2011) of twin studies (Hallmayer et al., 2011) performed between 1977 and 2011 concluded that the concordance rate for ASD in monozygotic twin pairs ranges from 36 % to 96 %, suggesting a contribution of environmental factors. A growing body of evidence implicates the maternal exposome during pre- and early postnatal development as a significant causal factor in the etiology of neurodevelopmental disorders.

One mechanism by which environmental exposures during early life can contribute to fetal programming is via epigenetic modifications in the developing fetus. By altering gene expression, epigenetic variations can have a significant impact on fetal development, a highly vulnerable process requiring a strict and precise regulation of gene expression at specific time points in specific tissues. The hypothesis that environmentally-induced shifts in the fetal epigenome can trigger fetal programming has gained ground in the scientific and medical communities, setting the stage for large-scale epigenomic studies. For instance, maternal obesity-induced changes in the fetal epigenome have been proposed to increase risk for metabolic disease in offspring (Rizzo et al., 2020). A similar hypothesis has been proposed for ASD risk (Mbadiwe and Millis, 2013; Wiśniowiecka-Kowalnik and Nowakowska, 2019), providing a potential rationale for the existence of disease-discordant monozygotic twin pairs; however,

further studies are required to fully elucidate the role of epigenetic variations in the context of neurodevelopmental disorders.

In addition to epigenetic modifications, environmental effects can be channeled through the maternal gut microbiome. Maternal factors, diet most strongly, shape the composition and community structure of the infant gut microbiome (Chu et al., 2016, 2017). During pregnancy, the maternal gut microbiome exerts a profound effect on fetal development and plays an important role in fetal programming (Jasarevic and Bale, 2019). Intriguingly, crosstalk between the maternal diet during pregnancy, the maternal microbiome, and the fetal epigenome has been proposed as one of the primary determinants of fetal programming and offspring susceptibility to disease (Li, 2018). While emerging evidence implicates multiple maternal environmental factors–including immune modulation, epigenetics, and gut microbiota–contribute to neurodevelopmental disorders, here we review evidence of the potential mechanisms by which maternal diet-induced dysbiosis of the gut microbiome could impair offspring brain development and contribute to phenotypes in neurodevelopmental disorders.

3. Diet-induced obesity and the maternal gut microbiome

In the United States (US), the obesity epidemic is now playing out not only in states and regions with a historically high prevalence of obesity, such as the Mississippi Delta and Southeastern US (Mills et al., 2020), but also in states with traditionally lower rates of obesity, like California (Mills et al., 2020; Ratnasiri et al., 2019). Interestingly, the recent rise in obesity rates in the US disproportionately affect women (Flegal et al., 2016)–between 2005 and 2015, obesity incidence increased by 5% in women but only 2% in men (Deputy et al., 2018; Flegal et al., 2016)–particularly those of childbearing age (Branum et al., 2016; Malik et al., 2013). Overnutrition is a leading factor behind the rising tide of obesity (body mass index [BMI] of 30.0 and over) in most high-income countries (Mozaffarian et al., 2011). Indeed, Western pattern diet (WPD), characterized by increased animal protein and sugar consumption with decreased complex carbohydrate intake, is the primary determinant of pathological weight gain in diet-induced obesity (Klurfeld and Kritchevsky, 1986; Mozaffarian et al., 2011). Several epidemiological studies demonstrate that BMI is positively correlated with risk of developing a wide range of diseases, such as diabetes, stroke, cardiovascular disease, and cancer (Afshin et al., 2017; Nyberg et al., 2018); however, obesity not only threatens the health of the individual, but significantly increases chronic disease risk in offspring (Davis, 2020; Godfrey et al., 2017).

Maternal overweight and obesity now affects two out of every five pregnancies in the US (Branum et al., 2016; Flegal et al., 2012). These epidemiological data represent a significant national health concern, given that maternal obesity during pregnancy is associated with several adverse short- and long-term health outcomes in offspring (Davis, 2020), including metabolic (Campodonico-Burnett et al., 2020; Eriksson et al., 2015; Hu et al., 2019; Naess et al., 2016; Nicholas et al., 2020; Wang et al., 2020), neuropsychiatric (Kong et al., 2020b; Mina et al., 2017; Panjwani et al., 2019), and neurodevelopmental disorders (Connolly et al., 2016; Contu and Hawkes, 2017; Godfrey et al., 2017; Jo et al., 2015; Kong et al., 2020b; Krakowiak et al., 2012), among others. They also underscore the importance of developing a more comprehensive understanding of the mechanisms by which maternal obesity jeopardizes offspring health. Simultaneously, they represent a yet unrealized opportunity for providing early life preventative care to a readily identifiable vulnerable population during a defined critical period in which most patients receive relatively frequent medical care and monitoring, the antenatal period. To develop effective means of targeting the maternal and/or offspring gut microbiome in the context of maternal obesity, it is critical to understand how obesogenic diets and host genetics modify gut microbial ecology.

Western pattern diet is associated with significant changes in the community structure of the gut microbiome of rodents (Bisanz et al., 2019), as well as human (Ley et al., 2006; Turnbaugh, 2017; Turnbaugh et al., 2008, 2006) and non-human primates (Ma et al., 2014). Notably, work from the Gordon Lab and others demonstrates that malnutrition also profoundly alters the gut microbiome, including a severe reduction in microbial diversity (Chen et al., 2020, 2021; Reyes et al., 2015), but here we focus on the effects of overnutrition.

Characterization of obese-type gut microbial ecology, by 16S ribosomal RNA (rRNA) gene amplicon sequencing, was first performed on distal cecal samples from mice homozygous for a mutation in the leptin gene (Lep^{ob};*ob*/*ob*), a genetic mouse model for obesity, and their lean counter parts, *ob*/+ and +/+ mice (Ley et al., 2005). 16S rRNA gene amplicon sequencing is a technique initially reported in 1999 to identify microbial species beyond those that could be readily cultured (Suau et al., 1999) that would prove fundamental to the NIH-sponsored Human Microbiome Project (Gevers et al., 2012; Turnbaugh et al., 2007). Despite vertical transmission of gut microbiota from the heterozygous dam, the microbiota composition of *ob*/*ob* mice significantly diverged from that of their *ob*/+ and +/+ littermates, revealing that host genetics could influence gut microbiome composition (Ley et al., 2005). High-fat diet-induced obesity similarly drives a significant shift in gut microbial ecology in both humans and animal models, with a characteristic plunge in microbial diversity (David et al., 2014; Turnbaugh et al., 2009). Several studies reporting metagenomic characterization of the gut microbiome composition in different mouse models of obesity identified an increase in the ratio of the two most prevalent bacterial phyla (Ley et al., 2006; Turnbaugh et al., 2006), the Firmicutes and Bacteroidetes [however, see (Magne et al., 2020)], which is associated with high levels of fatty acid synthesis substrates and increased capacity for energy harvest, primarily by altering hepatic lipid metabolism and microbial modulation of host genes that increase lipid storage in adipocytes (Turnbaugh et al., 2006). Yet, the identification of a precise microbial signature linked to obesity remains under investigation, due to both methodological variability of the different studies and biological variability of the hosts (Sze and Schloss, 2016).

Functionally, fecal microbiota transfer from obese mice to germ-free mice increases body weight and fat mass (Backhed et al., 2004; Rastelli et al., 2018; Turnbaugh et al., 2006), revealing a causal role in obese body mass composition phenotypes. Similarly, antibiotic administration reduced obesity and metabolic disorders in obese animals (Carvalho et al., 2017). Furthermore, fecal microbiota transplants (FMT) from human twins discordant for obesity resulted in reproduction of the donor phenotype in the recipient mice: mice that received an FMT from the lean twin remained lean, whereas mice that received an FMT from the obese twin became obese (Ridaura et al., 2013).

High-fat diet-driven decrease of gut microbial diversity (Kasai et al., 2015; Rampelli et al., 2018) is associated with obesity and low-grade inflammation, leading to 'leaky gut syndrome,' caused by dysfunctional tight junctions in the mucosal barrier (Hollander and Kaunitz, 2020). This in turn leads to increased translocation of bacterial products such as pro-inflammatory lipopolysaccharides (LPS), and bacteria themselves into the circulation, thus inducing systemic inflammation and detrimental effects in distant tissues and organs (Chakaroun et al., 2020). Additionally, a high-fat diet promotes overgrowth of bacteria which exert detrimental effects on the immune system, exacerbating inflammatory responses associated with intestinal disorders, autoimmune diseases in the central nervous system (CNS) (Haghikia et al., 2016), and cancer (Bishehsari et al., 2020).

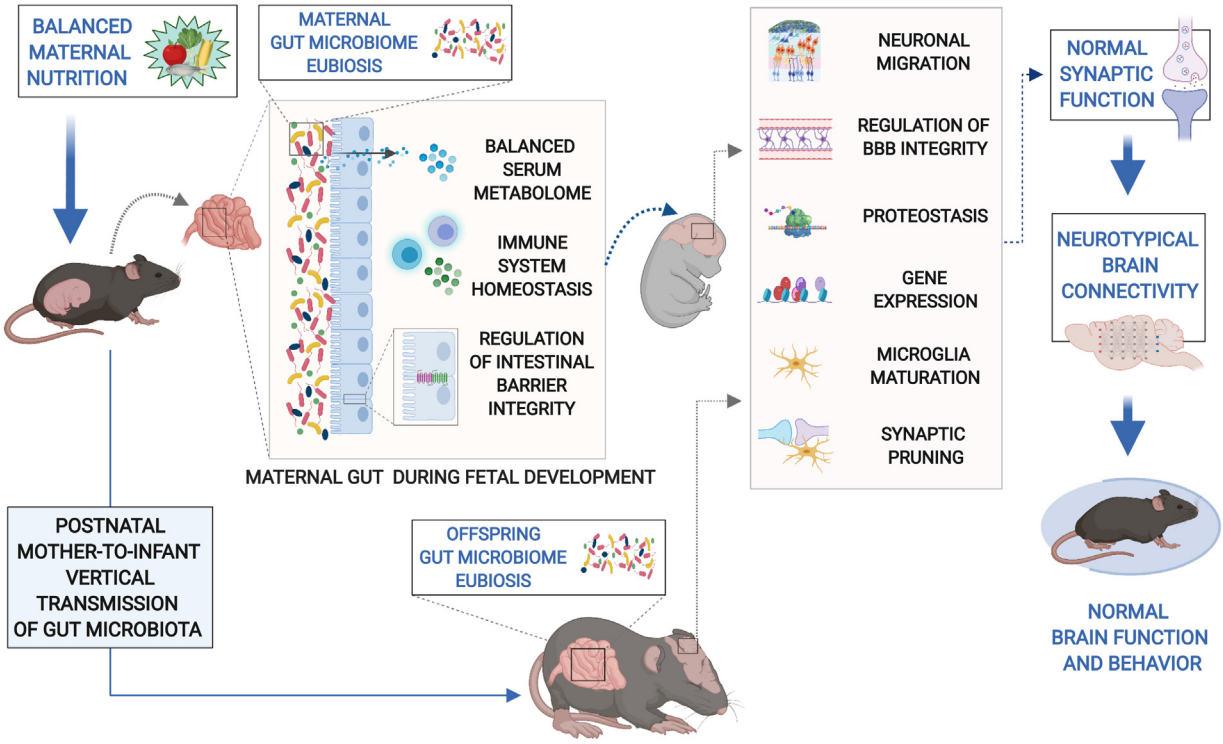

Fig. 1. Mechanisms mediating the influence of maternal gut microbiota on fetal and early postnatal brain development in offspring. Diet is a key factor determining the composition of the gut microbiota. In healthy individuals, a well-balanced and variegated diet is associated with a state of 'eubiosis' of the gut microbiome, which helps maintain immune system homeostasis, integrity of the intestinal barrier, and balance in the microbially-derived metabolites present in the host serum. During pregnancy, equilibrium of the interplay between the gut microbiota and host factors in the maternal environment is crucial for healthy fetal development, especially in the context of neurodevelopment. Indeed, by regulating maternal physiology, the gut microbiota influences many processes occurring in the developing fetal brain, such as neuronal migration, gene expression, protein synthesis, microglia maturation, among others. The influence of gut microbiota on brain development continues during early postnatal development, given that maternal gut microbiota are vertically transmitted to offspring after birth and participate in late stages of neurodevelopment, such as neural circuit formation and synaptic pruning via multiple channels mediating gut microbiota-brain communication. Both pre- and postnatal gut microbiota-mediated regulation of brain development is critical for synaptic function and brain connectivity, and, consequently, for brain function and behavior.

Divergence from gut microbial eubiosis during pregnancy (Fig. 1) necessitates a holistic view which considers diet-induced changes among both the maternal and offspring gut microbiome in the context of ante- and neonatal care. Beyond gestation, metagenomic characterization of the gut microbiome of human, non-human, and rodent offspring (Buffington et al., 2016; Chu et al., 2016; Ma et al., 2014) has revealed an enduring effect of maternal high-fat diet on the offspring gut microbiome with functional implications ranging from impaired metabolism to brain function (Fig. 2). While dysbiosis caused by direct high-fat diet feeding has been shown to be reversible (Turnbaugh et al., 2008), studies on the effect of diet-induced reductions in microbial diversity on subsequent generations have revealed compounding extinctions in microbial populations (Sonnenburg et al., 2016). Such diet-induced loss of microbial diversity can in turn be detrimental to the host, given that it limits host access to a rich repertoire of microbial genes essential to host functions, including energy harvest from food sources, and because low diversity environments can engender upregulation of opportunistic pathogenic species (Kamada et al., 2013). Indeed, low dietary fiber intake in mice has been shown to reduce overall microbial diversity and simultaneously decrease the amount of short-chain fatty acids (SCFAs) in host circulation in multiple studies (Daniel et al., 2021; Trompette et al., 2014). In contrast, increased dietary fiber intake enhanced microbial gene richness and improved clinical phenotypes in an obese human population (Cotillard et al., 2013). These findings highlight the importance of developing a comprehensive understanding of the impact of the industrialized gut microbiome on offspring health and effective means of restoring and maintaining a rich microbial ecosystem to thwart adverse health outcomes (Sonnenburg and Sonnenburg, 2019), such as those increasingly associated with maternal diet-induced obesity, including neurodevelopmental impairment.

4. Diet-induced dysbiosis of the maternal gut microbiome: neurodevelopmental implications

Given that gut microbiota are emerging as powerful regulators of host physiology (Clemente et al., 2012), including neurophysiology (Vuong et al., 2020, 2017), studies are beginning to explore the idea that diet-induced alterations in the maternal gut microbiome during pregnancy might ultimately lead to impaired fetal development, thus negatively affecting brain function and behavior (Cirulli et al., 2020; Vuong et al., 2020). The critical role of the maternal gut microbiome in fetal neurodevelopment was recently demonstrated in germ-free mice (Vuong et al., 2020). Thalamocortical organization, including axonal outgrowth and targeting, and related sensory processing was impaired in germ-free offspring. Colonization of the maternal gut with select species or treatment with specific microbially-derived metabolites restored the thalamocortical deficiencies, thus providing evidence for a fundamental requirement for microbial regulation of host fetal brain development and, ultimately, behavior.

Maternal micro- and macronutrient intake have a strong impact on fetal development. Likewise, availability of macronutrients during pregnancy shapes the maternal microbial community. However, the importance of maternal diet is not limited to the gestational period but also bookends it, extending from the pre- and periconception period, for processes such as gamete function and placental growth, to the postnatal period, particularly in

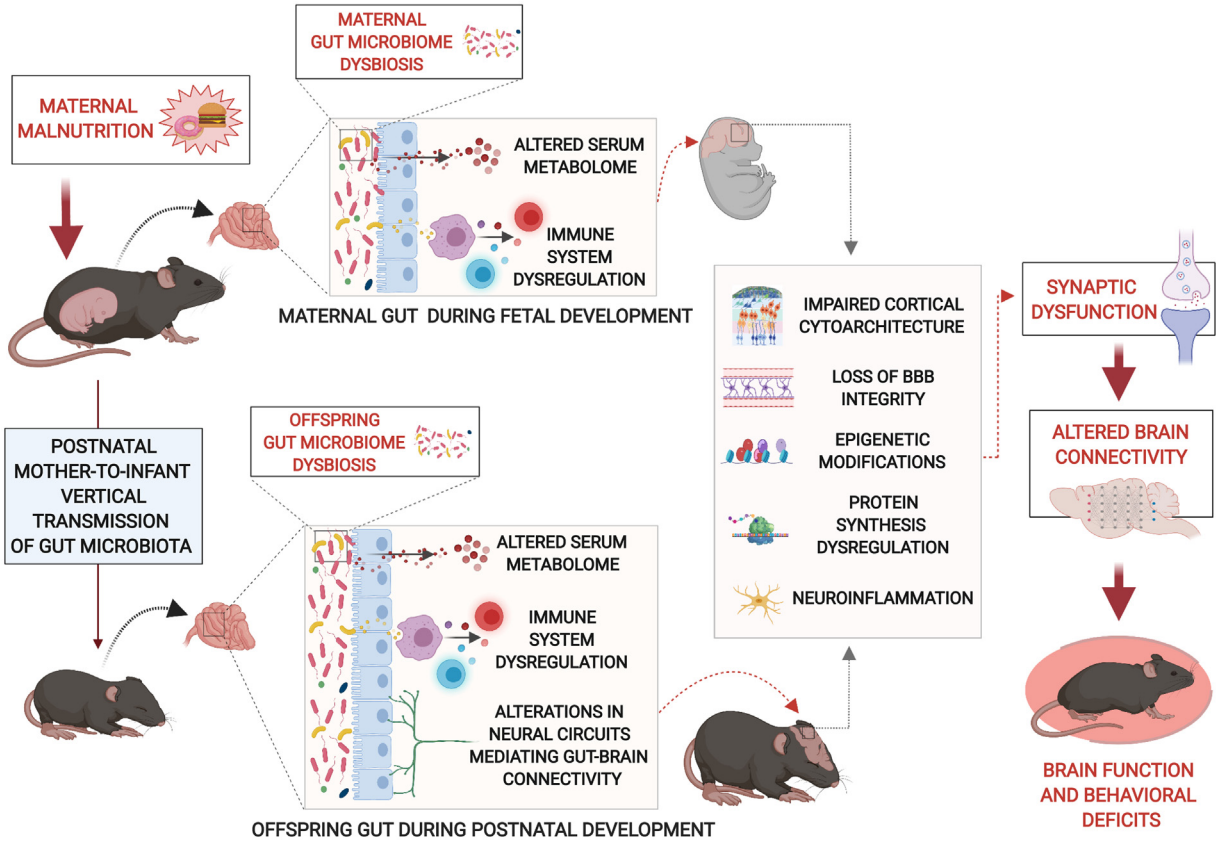

Fig. 2. Mechanisms mediating the negative effects of diet-driven dysbiosis of the maternal gut microbiota on fetal and early postnatal brain development in offspring. During fetal development, maternal overnutrition-driven dysbiosis of the maternal gut microbiome, manifested as a decrease in alpha diversity and changes in the relative abundance of some microbial species, drives immune system dysregulation and alterations in microbially-derived serum metabolites. These diet-driven changes in the maternal environment are proposed to negatively impact the developing fetal brain by leading to impairments in cortical neuron migration and resulting cortical dysplasia, loss of brain-blood-barrier integrity, altered gene expression and protein synthesis, and increased neuroinflammation, among other effects. Given that maternal gut microbiota are vertically transmitted to offspring after birth, the detrimental effects of diet-driven dysbiosis of the gut microbiome are extended to postnatal offspring neurodevelopment. Indeed, inheritance of dysbiotic gut microbiota from the mother can lead to dysregulation of the offspring serum metabolome, immune system dysfunction, and alter neural circuits mediating gut-brain connectivity, thus jeopardizing postnatal brain development. The combined effect of pre- and postnatal microbiota-mediated dysregulation of neurodevelopment can lead to synaptic dysfunction and altered brain connectivity, ultimately contributing to the onset of deficits in brain function and behavior.

breastmilk-fed infants. Multiple studies suggest a U-shaped correlation between unbalanced maternal diet and increased risk for disease in the offspring. Indeed, either deprivation (undernutrition) (Hoek et al., 1998; King, 2016; St Clair et al., 2005) or excess (overnutrition) (Kong et al., 2020a) of maternal nutrient intake at conception and throughout pregnancy can trigger fetal programming phenomena.

Initial investigations into the relationship between ASD and the gut microbiome grew out of patient and parental reports of gastrointestinal (GI) distress. Most individuals affected by ASD experience common comorbidities–in fact, a growing number of studies support the idea that many symptoms usually considered additional features of ASD are in fact related to other disorders which should be diagnosed as comorbid conditions. The presence of comorbidities generally leads to more pronounced behavioral and cognitive deficits (Gadow et al., 2012). Neuropsychiatric disorders are often associated with ASD (Hossain et al., 2020; Romero et al., 2016). Less expectedly, GI dysfunction is frequently observed in children with ASD (Madra et al., 2020), with reported prevalence varying from 9% to 91 % (Buie et al., 2010). ASD subjects are four times more likely to display GI disturbances, compared to non-ASD subjects, with diarrhea, constipation, and abdominal pain the most frequent ones (McElhanon et al., 2014). The presence of GI disturbances correlates with severity of behavioral and cognitive phenotypes in ASD (Wang et al., 2011). Consistently, GI dysfunction is commonly cited in parental reports (Gorrindo et al., 2012) and its severity is positively correlated with that of behavioral symptoms (Aldinger et al., 2015).

The co-occurrence of ASD with GI dysfunction has prompted recent investigation into the mechanistic relationship between the two, seemingly etiologically unrelated, conditions. This has led to ongoing studies into the gut microbiome composition of ASD patients as well as microbial-based treatments, including fecal microbiota transplants. An open-label study of Microbiota Transfer Therapy (MTT) (Kang et al., 2017) investigated the effects of FMT to children with ASD and chronic gastrointestinal disturbances, and a follow-up study (Kang et al., 2019), conducted two years after the treatment stopped, assessed the long-term effects of this treatment. Marked improvements were observed in each of the 18 participants, with reductions in both behavioral and GI symptomatology, which persisted at least two years. Despite promising results, FMT has not gained full approval from the US Federal Drug Administration (FDA), which expressed concerns regarding the potential presence of drug-resistant bacteria in the fecal matter. This scenario highlights the complexities of human-to-human fecal microbiota transplant and provides compelling rationale for identifying probiotic species that can be prepared as pure cultures and delivered prophylactically.

Maternal obesity, excess gestational weight gain, and diabetes are associated with increased risk of neurodevelopmental deficits in offspring. For instance, both maternal obesity (Dodds et al., 2011; Krakowiak et al., 2012; Reynolds et al., 2014; Shen et al., 2018;

Wang et al., 2016) and diabetes (Wang et al., 2016; Xu et al., 2014) have been reported as risk factors for ASD, with potentially greater risk when mothers are affected by both obesity and diabetes (Kong et al., 2018; Li et al., 2016). Similar findings are reported for other neurodevelopmental disorders broadly characterized by impairment of social skills and/or intelligence, such as attention deficit hyperactivity disorder (ADHD) (Chen et al., 2014; Rodriguez et al., 2008), intellectual disability (ID) (Li et al., 2016), global developmental delay (GDD) (Duffany et al., 2016), and for those related to deficits in specific developmental domains (Krakowiak et al., 2012), including motor disorders (Wylie et al., 2015) and communication disorders (Dionne et al., 2008). However, a major limitation of epidemiological studies is the effect of potential confounding factors, such as genetic background and postnatal environment, which might distort interpretation of the association between the environmental exposure and specific health outcomes. For these reasons, epidemiological findings are complemented by animal studies which can provide important insights into molecular mechanisms underlying the maternal diet-induced risk for ASD and other neurodevelopmental disorders.

Animal models of diet-induced obesity are widely used to assess the impact of maternal obesity and metabolic conditions on offspring neurodevelopment and mental disorders. A commonly used murine model of maternal diet-induced obesity involves the administration of a high-fat regimen to female mice for a number of weeks before mating and conception (Al Nabhani et al., 2019; Bilbo and Tsang, 2010; Buffington et al., 2016). Exposure to MHFD induces deficits in offspring social behavior (Buffington et al., 2016; Kang et al., 2014) and learning and memory (Mucellini et al., 2019; Noble and Kanoski, 2016; Wolfrum and Peleg-Raibstein, 2019) as well as impairments in synaptic plasticity (Lin et al., 2021), neurogenesis (Stachowiak et al., 2013; Tozuka et al., 2009), and neuronal connectivity (Arikkath, 2012). Yet, the precise mechanisms underlying the impact of maternal diet on offspring neurodevelopment remain to be determined. Multiple mechanisms and pathways have been proposed to explain the connection between maternal diet and offspring health outcomes, such as inflammation (Bilbo and Tsang, 2010), epigenetic modification (Godfrey et al., 2017), and, more recently, alterations in the gut microbiome (Al Nabhani et al., 2019; Buffington et al., 2016; Ma et al., 2014; Zhang et al., 2019) – a hypothesis explored in depth in this review.

5. Mechanisms by which obese-type maternal gut microbiota could affect neurodevelopment

The prenatal and early postnatal periods are critical windows in human growth and development during which exposure to harmful environmental factors can exert a broad impact on developmental processes. A growing body of work is dedicated to investigating the connection between the pregnancy exposome and fetal development, especially neurodevelopment. Here, we highlight three primary channels mediating communication along the gut-microbiota-brain axis by which diet-induced dysbiosis of the maternal gut microbiome could impair offspring brain development, with consideration of the fetal and early postnatal periods.

5.1. Microbial regulation of host immune function during the prenatal and early postnatal periods

To begin to probe the mechanisms underlying developmental neuropathology associated with maternal diet-induced dysbiosis of the gut microbiome, it is helpful to consider the case of maternal immune activation (MIA), which models clinical data demonstrating that infants born to women hospitalized for infection during pregnancy are at elevated risk for neurodevelopmental disorders, including ASD (Lee et al., 2015, 2019). Over 20 years (Shi et al., 2003) of investigation in rodent and non-human primate models of MIA [notably, the subject of a campaign toward increased consistency (Kentner et al., 2019)] point to the maternal immune response as a key determinant of the effect of prenatal immune challenge on fetal brain development (Estes and McAllister, 2016). Importantly, increased risk of neurodevelopmental disorders associated with maternal infection appears to be the result of pathological MIA and related inflammatory responses that damage the developing fetal brain, independent of the specific class of pathogen (*e.g.*, of viral versus bacterial origin) (Abdallah et al., 2012; Brown et al., 2014; Estes and McAllister, 2015; Jiang et al., 2016).

Core ASD-like behaviors have been observed in offspring of MIA preclinical models of maternal infection during pregnancy. In mouse studies employing the MIA model, immune activation is often induced mid-gestation (E12.5) via intraperitoneal injection of the viral mimetic polyinosinic:polycytidylic acid (poly(I:C)). Like maternal high-fat diet consumption (Buffington et al., 2016), MIA has also been shown to alter the offspring gut microbiome (Hsiao et al., 2013).

While the aforementioned studies provide important insight into the role of immune dysregulation in offspring brain development and behavior, until recently the field had, for the most part, overlooked the role of the microbiome in regulating maternal immune homeostasis as well as prenatal development, reviewed extensively in (Jasarevic and Bale, 2019). In fact, recent studies identify maternal gut bacteria as critical mediators of maternal inflammation-induced neurodevelopmental pathology underlying MIA offspring behavioral dysfunction and causally implicate pathological maternal interleukin-17a (IL-17a) pathway activation (Choi et al., 2016; Hsiao et al., 2013; Kim et al., 2017; Shin Yim et al., 2017). Pathological activation of the pro-inflammatory IL-17a pathway in C57Bl/6N female mice injected with poly(I:C) at E12.5 leads to abnormal cytoarchitecture in the socially relevant dysgranular zone of the primary somatosensory cortex (S1DZ) and resulting behavioral abnormalities in offspring (Choi et al., 2016; Shin Yim et al., 2017). Intriguingly, the neurodevelopmental disorder-like phenotypes observed in the MIA offspring are dependent on the presence of segmented filamentous bacteria (SFB) in the maternal gut, since offspring of SFB-negative C57Bl/6J mice are refractory to the poly(I:C)-induced behavioral deficits (Kim et al., 2017). Given that obesity is associated with chronic low-grade inflammation and that a high-fat diet compromises intestinal barrier function that can be reversed by the anti-inflammatory cytokine IL-22 (Gulhane et al., 2016), it is reasonable to hypothesize that maternal diet-induced obesity could cause similar pathological activation of the maternal immune system and, consequently, compromise offspring brain development and behavior.

In utero, the maternal microbiome also has an important role in defining fetal microglial physiology, which directly impacts neural circuit formation. This was elegantly demonstrated by Thion et al., who showed that in the absence of gut microbiota (as in the case of germ-free mice), shifts in embryonic microglial gene expression occur as early as E14.5, but more dramatically at E18.5, with males being more affected (Thion et al., 2018). Of note, differentially expressed genes in males *vs.* females included those involved in inflammation, further highlighting the connection between the microbiome and immune system, and potentially providing contributing rationale as to why males are more susceptible to ASD (Fombonne, 2009; Loomes et al., 2017).

Although the uterus, like the brain, is immunologically privileged, circulating maternal factors nonetheless reach the placenta, the amniotic fluid, and the fetus itself (Urakubo et al., 2001). For instance, pro-inflammatory cytokines, hormones, and other high-fat diet-induced signaling molecules cross the placenta and reach the fetus, contributing to the impairment of neural pathways

underlying behavior and cognition (Piazza et al., 2019), including serotoninergic (Thompson et al., 2017) and dopaminergic (Aguilar-Valles et al., 2012) circuits, and the hypothalamic-pituitary-adrenal (HPA) axis (Bellisario et al., 2015). Additionally, maternal cytokines, including interleukin 6 (IL-6) (Friis et al., 2013) and tumor necrosis factor alpha (TNF-alpha) (Siwetz et al., 2016), and adipokines (Duval et al., 2016) influence placental nutrient transport and nutrient delivery to the fetus (Sureshchandra et al., 2018). Together, these data support a direct impact of maternal gut dysbiosis-induced inflammation on fetal brain development.

Postnatally, analysis of the infant gut microbiome of healthy controls *versus* those at risk for type I diabetes revealed three phases of development: a developmental phase, transitional phase, and stable phase converging around 31 months (Stewart et al., 2018). Chu et al. and others reported that 16S rRNA gene amplicon sequences from neonatal stool cluster together based on maternal diet (Chu et al., 2016, 2017; Galley et al., 2014); however, others have shown that development of the infant microbiome over time is multifactorial and does not cluster by a single maternal factor (Raspini et al., 2021). Regardless, microbial colonization of the host's mucosa early in life profoundly shapes the maturation and balance of the immune system (Backhed et al., 2015). Consistent with this hypothesis, changes in the microbiome of ASD patients (Finegold et al., 2010) and increased pro-inflammatory cytokine levels in ASD patient sera (Masi et al., 2017) have been observed, though no common "ASD gut microbiome" exists. In germ-free mice, Thion et al. found that microglial density at postnatal day 20 was increased in the striatum, the somatosensory cortex, and the preoptic area compared to specific pathogen free mice (Thion et al., 2018). In non-human primates, Ma et al. provide evidence that HFD during pregnancy elicits offspring gut dysbiosis that cannot be fully corrected with control diet post-weaning (Ma et al., 2014). Taken together with transgenerational extinctions that reduce alpha diversity across generations in HFD-fed rodents (Sonnenburg et al., 2016), these findings underscore the importance of enriching alpha diversity of the maternal gut microbiome to promote offspring health during fetal and early postnatal development and of acting now to conserve and sustain healthy gut communities jeopardized by an industrialized environment (Sonnenburg and Sonnenburg, 2019).

5.2. *Microbially-derived metabolites in fetal and early postnatal brain development and behavior*

Host diet determines nutrient availability to the microbiota, and therefore, continually shapes microbiota composition, which is then reflected in the global microbial metabolome. This collection of microbially-derived metabolites has pleiotropic effects on host function, both in physiological and pathological states. The influence of maternal microbially-derived metabolites is extended to the fetus during the gestational period; therefore, the composition and community structure of the maternal gut microbiome is critical to proper fetal growth and development (Koren et al., 2012). Maternal obesity induces significant changes in the composition of the gut microbiome, which in turn alter the microbially-derived metabolite profile in both the mother and developing fetus. Such alterations are poised to significantly impact fetal development and contribute to fetal programming (Calatayud et al., 2019; Jasarevic and Bale, 2019). Among microbially-derived metabolites (Needham et al., 2020), neurotransmitters and their precursors, short chain fatty acids (SCFAs)–acetate, butyrate, and propionate–, and branched-chain amino acids (BCAAs)–valine, leucine, and isoleucine–have gained a great deal of attention because of their broad influence over various host processes, including those involved in the regulation of brain function and behavior.

Neurotransmitters and neuropeptides play an important role in regulating the gut-microbiota-brain axis. Neuropeptides, including substance P, calcitonin gene-related peptide, neuropeptide Y (NPY), somatostatin, and others, contribute to the regulation of the mutual relationship between the microbiota and the host. Neuropeptides can modulate the activity of gut microbiota and, conversely, microbial control of amino acid availability and gut hormone release regulates the synthesis of neuroactive peptides (Holzer, 2016). Similarly, neurotransmitters exert pleiotropic effects on the gut microbiome, and, interestingly, the gut microbiota itself is a source of neurotransmitters–dopamine, norepinephrine, gamma-aminobutyric acid (GABA), serotonin, and histamine are each synthesized by gut-residing microorganisms (Strandwitz, 2018).

Altered levels of fecal SCFAs are associated with several brain disorders, including ASD (Liu et al., 2019; Wang et al., 2012). The serum concentration of SCFAs, which promote intestinal barrier integrity and modulate intestinal inflammation (Lewis et al., 2010; Peng et al., 2009), for example, is elevated by high-fat diet consumption (Turnbaugh et al., 2006). SCFAs also cross the intestinal mucosal barrier and can be transported through the blood stream to host cells, where they are metabolized as an energy source via the Krebs cycle. Additionally, SCFAs also play multiple signaling roles in the context of the gut-brain axis, summarized in (Dalile et al., 2019). Indeed, SCFAs affect brain physiology through multiple indirect mechanisms, and it is possible that they cross the blood–brain barrier, as a result of elevated expression of monocarboxylate transporters MCTs on endothelial cells (Mitchell et al., 2011). Lastly, SCFAs, especially butyrate, can enhance the inhibitory effect of histone deacetylase, which has been implicated in the pathogenesis of neuropsychiatric disorders (Volmar and Wahlestedt, 2015). Acute doses of butyrate have been proven to ameliorate cognitive deficits (Fischer et al., 2007; Levenson et al., 2004) and ASD-like social dysfunction (Kratsman et al., 2016) in animal models.

SCFAs bind to several G protein-coupled receptors (GPCR), such as GPR43 and GPR41, later renamed free fatty acid receptor 2 (FFAR2) and FFAR3 (Brown et al., 2003). FFAR3 is expressed in the PNS and at the BBB. Propionate-induced FFAR3 activation of vagal fibers increases activity of the dorsal vagal complex, parabrachial nuclei, and hypothalamus (De Vadder et al., 2014). These data suggest that SCFAs can directly influence brain activity through the vagus nerve. SCFAs also stimulate enteroendocrine signaling–FFARs receptors are expressed on colonic enteroendocrine L cells, and their activation leads to the production of GLP-1 and PYY in the circulation (Larraufie et al., 2018; Tolhurst et al., 2012). Each of these hormones directly regulates appetite and food intake in the CNS (Alvarez et al., 2005; Nonaka et al., 2003). In mice, GLP1 improved learning and memory (During et al., 2003), and increased neuroplasticity and reduced microglia activation; however, additional studies will be required to unravel the complex effects of SCFAs on brain function and behavior.

Branched chain amino acids (BCAAs) are essential amino acids which must be introduced via the diet or produced by microbiota. They are key nitrogen donors that play an important role in intercellular and interorgan nitrogen transfer. A growing body of evidence suggests that BCAAs play essential roles in the regulation of several biochemical mechanisms beyond simple nutrition (Monirujjaman and Ferdouse, 2014). Unlike other AAs, BCAAs are not metabolized in the liver (Sweatt et al., 2004), but instead their oxidation [transamination via the branched-chain aminotransferases (BCAT) isozyme] initially occurs in peripheral tissues, especially in skeletal muscle (SK), where they can modulate several physiological processes, such as protein synthesis and degradation, glucose homeostasis, hormonal regulation and nutrient-sensing signaling pathways, including, phosphoinositide 3-kinase-protein kinase B (PI3K-AKT), the mammalian target of rapamycin (mTOR) pathways. Transamination is followed by irreversible oxidative

decarboxylation of the α-keto acid products, which is catalyzed by the branched-chain α-keto acid dehydrogenase enzyme complex (BCKDC) in the liver.

BCAAs can stimulate initiation of mRNA translation and reduce protein degradation (Kimball and Jefferson, 2001). The mechanism by which BCAAs stimulate protein synthesis is thought to involve the mTOR translational control pathway (Hay and Sonenberg, 2004). Among the three BCAAs, leucine (Anthony et al., 2000) is the most effective in increasing mRNA translation through the phosphorylation and subsequent activation of the main effectors of the mTOR pathway, elF4E-BP1 and p70 S6 kinase. In the context of glucose homeostasis, BCAAs stimulate glycogen synthesis (Peyrollier et al., 2000) and glucose uptake by SK and liver by insulin-independent mechanism which involves PKC and PI3-kinase pathways rather than the mTOR pathway (Nishitani et al., 2002). The CNS is very sensitive to AA and nitrogen levels because either deprivation or accumulation of AAs can be toxic and disrupt protein synthesis and neurotransmitter production in the brain. Plasma BCAAs are transported into the brain and other regions of the CNS by means by a transporter, located at the blood–brain barrier (BBB) on CNS capillary endothelial cells, shared by many large neutral amino acids, such as aromatic amino acids (ArAAs) tryptophan, tyrosine, and phenylalanine (Fernstrom, 2005). BCAAs are also nitrogen donors in glutamate and glutamine brain metabolism.

While BCAAs are required for protein and neurotransmitter synthesis as well as energy production in the brain, exaggerated intake of BCAAs can cause neurotoxicity. Maple syrup urine disease (MSUD) (Chuang et al., 2015), for example, is an inherited disorder of BCAA catabolism, manifested as abnormal increase of BCAA concentration in blood, cerebrospinal fluid, and urine, and characterized by cognitive dysfunction (Zinnanti and Lazovic, 2012). The detrimental effects of elevated BCAA levels on neuronal cells are further demonstrated by studies (Carunchio et al., 2010; Contrusciere et al., 2010) reporting hyperexcitability of cortical neurons by BCAAs which leads to excitotoxicity. High BCAA levels also impair the function of microglia, the primary macrophage population in the brain, which can contribute to neurotoxicity and aberrant synaptic pruning. Indeed, microglia can either increase or attenuate an inflammatory response, by acquiring pro- (M1) or anti-inflammatory (M2) phenotypes. Intriguingly, some studies (De Simone et al., 2013) found that high levels of BCAAs can promote the acquisition of a phenotype which is an intermediate between M1 and M2 and might lead to a low-grade inflammatory state.

BCAAs are also implicated in numerous physiological and pathological processes in the body, such as immune pathways. Immune cells can internalize BCAAs and oxidize them (Calder, 2006). BCAA deficiency causes impairments in innate immunity, especially in the intestinal mucosa, and reduces resistance to pathogens (Ma et al., 2018). Growing interest in metabolic regulation of the immune response prompted the investigation of the role of BCAAs in T cell activation and function (Ananieva et al., 2016). Specifically, leucine is proposed to be critical for mTORC1-mediated regulation of T cell activation and differentiation. One of the main enzymes responsible for BCAA metabolism is the cytosolic branched-chain aminotransferase (BCATc), which plays an important role in negative feedback regulation of the mTORC1 pathway. Loss of BCATc increases leucine availability, which in turn determines T cell hyperactivation (Ananieva et al., 2014).

BCAA dysregulation has been implicated in metabolic and neuropsychiatric disorders, including insulin resistance (IR), type 2 diabetes (T2D), and mental disorders, such as ASD. High levels of BCAAs have been associated with increased risk for metabolic abnormalities and development of IR (Asghari et al., 2018; Pedersen et al., 2016) and have been suggested to be an indicator of prediabetes (Gannon et al., 2018). Indeed, one of the effects of elevated BCAAs is the hyperactivation of mTOR/p70S6K pathway and phosphorylation of IRS-1 on multiple serine sites, which is thought to contribute to IR and cardiovascular disease (Uddin et al., 2019). BCAA dysregulation has also been proposed to contribute to the pathogenesis of maternal environmental factor-associated and syndromic autism. Indeed, studies (Chuang et al., 2015) found that the risk for ASD was increased in children, boys in particular, whose mothers presented with metabolic conditions and elevated BCAA levels during pregnancy (Panjwani et al., 2019). Additionally, coding variants in the large amino acid transporter gene, which is responsible for the transportation of tryptophan and BCAA across the blood-brain barrier, have been found in ASD patients (Cascio et al., 2020; Tarlungeanu et al., 2016). As mentioned above, BCAAs are essential amino acids that must be either supplied by diet or microbiota. Select microorganisms living in the gut carry the full complement enzymes necessary for BCAA synthesis, and BCAAs are essential for the growth and survival of many bacterial species. Components of the BCAA synthesis pathway have, consequently, been proposed as targets for the development of new antibacterial agents, due the fact that this pathway is not present in mammals, which may reduce toxicity (Amorim Franco and Blanchard, 2017).

Since microbiota can both synthesize and metabolize BCAAs, they can be considered as a master regulator of BCAA homeostasis in the host (Agus et al., 2020). Further investigation is required to better elucidate the role of BCAAs in the pathogenesis of environmentally induced neurodevelopmental disorders.

Additional microbially-derived low molecular weight metabolites are also key to host brain function and behavior. For instance, tetrahydrobiopterin (BH_4), an essential cofactor in dopamine synthesis, was found to be reduced approximately 20-fold in fecal samples collected from the *Cntnap2* mouse model for neurodevelopmental disorders (Buffington et al., 2021). Treatment of the mutant mice with BH_4 rescued the social deficits in the homozygous *Cntnap2* line, whereas treatment with a potent inhibitor of BH_4 synthesis impaired social behavior in WT mice. Taken together, these results demonstrate the power of metabolomic studies of disease states to provide key mechanistic insight into normal brain function.

The application of multi-OMICs is critical to advancing our mechanistic understanding of host-microbe interactions. Significant advances in culture-independent genomic techniques, such as shotgun metagenomics-based methods (Jovel et al., 2016), to precisely interrogate the myriad organisms–bacteria, viruses, and fungi–residing in the host gut have been made in recent years. However, these approaches are limited to the analysis of genomic material and do not include other features of microbial life, such as the transcriptome, proteome, and metabolome, which are crucial to the comprehension of the complex microbial physiology and its dynamic interaction with the host (Franzosa et al., 2015). Coupling predictive functional metagenomics with metabolomic approaches can provide functional insight, including identification of key therapeutic targets (Buffington et al., 2021), into microbial metabolic pathways contributing to host health and disease.

Resources such as the Kyoto Encyclopedia of Genes and Genomes (Goto et al., 1997; Kanehisa and Goto, 2000) and PICRUSt2, developed for predicting functional genomics based on marker gene sequences generated by 16S rRNA gene amplicon or other marker gene sequencing (Douglas et al., 2020; Langille et al., 2013), are frequently used for predictive functional metagenomics. The accuracy of such inference-based metagenomic predictions can vary between host species and sample types (Sun et al., 2020), highlighting the importance of a combined approach of predictive metagenomics with empirical metabolomics on host samples.

Metaproteomics (Zhang et al., 2017), for example, employs high-resolution mass spectrometry (MS) to characterize microbial protein compositions. Metabolomics approaches (Lamichhane et al., 2018) based on nuclear magnetic resonance (NMR) spec-

troscopy or MS allow for the analysis of fecal or microbial intracellular metabolites. Increasingly sophisticated MS-based approaches, including MS imaging (MSI), provide quantitative measurements of proteins produced by gut microbes, including host proteins and can do so with regional specificity (as is the case for MSI). Several metabolites present in the gut are produced and secreted by host-microbiome co-metabolism, and often serve as signaling molecules for communication between the two compartments (Nicholson et al., 2012).

Ultimately, combining metabolomics with host and microbial genetics, as well as neuronal activity and complex behavioral analysis, will be required to determine the precise mechanisms by which gut microbiota modulate host behavior, and their contributions to behavioral symptoms in neurodevelopmental disorders.

5.3. Neural circuits mediating gut-brain communication in fetal and early postnatal development

The gut is directly innervated by components of the autonomic nervous system (ANS), including the enteric nervous system (ENS) and the parasympathetic nervous system (PSNS), to which the vagus nerve (VN; cranial nerve X) belongs. These neuroanatomical pathways between the gut and brain allow for both rapid sensory transduction and relatively slow-acting enteroendocrine signaling between the gut and brain. Consequently, their function is key to maintaining intestinal homeostasis and gut-brain crosstalk. These neuroanatomical pathways epitomize the inherent complexity of gut-brain communication, given that their activity is reciprocally modulated through interaction with the host immune system and microbially-derived metabolites, thus posing a challenge to teasing out the precise mechanisms by which any single species or even consortium of microbiota impact host physiology. Yet, recent work performed in germ-free mice and using sophisticated neurosurgical techniques to sever connections have begun to shed light on these critical gut-brain circuits.

The ENS, a division of the peripheral nervous system (PNS), is an important neuronal network positioned at the intersection between the host and the microorganisms living in the gut. ENS maturation occurs during the postnatal stage, at the same time the microbiota colonizes the gut, and is itself influenced by the microbiota (Foong et al., 2020). Changes in the gut microbiome are reflected in ENS function: experiments in germ-free mice show that the absence of gut microbiota alters ENS excitatory properties, which can be restored by gut colonization (McVey Neufeld et al., 2013). Administration of commensal species, such as *Lactobacillus reuteri (L. reuteri),* modulate the excitability of ENS neurons (Kunze et al., 2009), and discrete microorganisms (Mao et al., 2013) exert different effects on ENS neuronal activity that are the result of distinct mechanisms, thus supporting an important role for the microbiota in ENS development and function. In light of recent studies showing the detrimental effect of maternal malnutrition on gut microbiota composition and fetal development, it is reasonable to hypothesize that maternal diet-driven dysbiosis in the maternal and offspring gut microbiome might compromise offspring ENS maturation and function.

The vagus nerve is the most direct neuroanatomical connection between the gut and the brain. In the gut, vagal fibers are located: (1) in the smooth muscles lining the gut, (2) within the mucosal layer without crossing the epithelium, and (3) in proximity of enteroendocrine cells (EECs). Consequently, vagal terminals do not come in direct contact with the microorganisms residing in the lumen; nonetheless, the VN senses changes occurring in luminal microbial populations. Advances in single-cell molecular analyses and monosynaptic tracing of neuroepithelial connections helped shed a light on neural circuits mediating VN luminal sensing. Bohórquez and colleagues recently identified a population of EECs expressing presynaptic cell adhesion molecules, then introduced a modified rabies virus into the colonic lumen to allow for identification of direct synaptic connections of the presynaptic protein-expressing EECs, which they coined “neuropod cells” (Kaelberer et al., 2018). Optogenetic activation of neuropod activity increased firing activity of the nodose ganglia, whereas inhibition attenuated sucrose sensing by nodose ganglia. To our knowledge, the function of neuropod cells beyond a eubiotic state in mice has yet to be explored, but we speculate that dysbiosis of the gut microbiome could alter sensory conduction between the neuropod cells and the brain. Furthermore, we postulate that genetic mutations associated with neurodevelopmental disorders that impair synaptic function and/or action potential propagation, may underlie some instances of comorbid gastrointestinal distress and potentially host genetics-induced dysbiosis of the gut microbiome.

The crucial importance of bidirectional connectivity mediated by the vagus nerve for normal brain function and behavior has been revealed by recent work in rodent models (Bohorquez et al., 2014; Han et al., 2018; Kaelberer et al., 2020). Indeed, either partial or total vagotomy have been shown to induce alterations in brain function associated with various neuropsychiatric disorders, such as anxiety-like and fear-related behavior (Klarer et al., 2014), learning (Klarer et al., 2017), locomotor activity (Itoh et al., 1981), and sensorimotor gating (Klarer et al., 2018). Other studies suggest that gut microorganisms can modify brain function via vagal fibers. For instance, *Campylobacter jejuni* administration in mice induces c-Fos activation, a marker of intense neuronal activity, in the VN (Goehler et al., 2005), and can increase anxiety-related behavior (Lyte et al., 1998). Similarly, *Lactobacillus* (*L.*) *rhamnosus* supplementation increased the firing rate of vagal afferents (Perez-Burgos et al., 2013) and reduced anxiety- and depression-related behavior in mice, an effect abolished by bilateral subdiaphragmatic vagotomy (Bravo et al., 2011). Members of the genus *Bifidobacterium* (*B.*), which pioneer the infant gut microbiome (Fehr et al., 2020), likewise exert anxiolytic effects on host behavior that are dependent on vagal nerve integrity. *B. longum* (NCC3001), for example, has been shown to exert an anxiolytic effect that was attenuated by vagotomy in a mouse model of infectious colitis (Bercik et al., 2011). Microelectrode recordings on excised ileal tissue revealed that *B. longum* decreased excitability of myenteric neurons; while the underlying molecular mechanism remains to be fully resolved, *B. longum* does produce limited amounts of the inhibitory neurotransmitter GABA. *Bifidobacteria* have also been shown to modulate brain function by promoting the synthesis of other neuroactive metabolites. Indeed, recent studies in germ-free mice demonstrated that *B. dentium* mono-association stimulates production of the neurotransmitter serotonin (5-hydroxytryptamine [5-HT]) from intestinal enterochromaffin cells and significantly increased hippocampal expression of serotonin receptor 2a (5-HT_{2a}) (Engevik et al., 2021). The primary source of *Bifidobacteria* in infancy is likely maternal breastmilk. In a recent cross-sectional human study, microbial diversity (*Bifidobacteria* abundance, in particular), was significantly reduced in the breastmilk of women that were overweight prior to pregnancy. The breastmilk microbiome, which is notably less well-studied than the gut microbiome but similarly poised to significantly influence fetal brain development and behavior (Bode et al., 2020), is also critically related to maternal diet and metabolic status and warrants further study.

Recent investigation into social dysfunction in mouse models for neurodevelopmental disorders (Buffington et al., 2016; Sgritta et al., 2019) revealed a central role for vagal terminals in the etiology of maternal environmental factor-associated social behavioral deficits. In mice, maternal high-fat-diet (MHFD) consumption throughout gestation and lactation induces dysbiosis in the maternal and offspring gut microbiome which is causally related to offspring social dysfunction. Unbiased metagenomic whole shot-

gun sequencing of MHFD fecal microbiota revealed a significant reduction in abundance of the commensal *L. reuteri*. Interestingly, *L. reuteri* promotes hypothalamic oxytocin (OT) production (Buffington et al., 2016; Poutahidis et al., 2013). OT, a hormone associated with social behavior (Donaldson and Young, 2008; Froemke and Young, 2021) and implicated in ASD pathology (Lerer et al., 2008; Wu et al., 2005), plays a crucial role in promoting synaptic plasticity in the ventral tegmental area (VTA), a dopaminergic reward circuit locus in the brain critically involved in social behavior (Gunaydin et al., 2014; Hung et al., 2017). Precision microbial reconstitution with *L. reuteri* restored hypothalamic OT, rescued synaptic plasticity in the VTA, and ultimately corrected MHFD offspring deficits in social behavior. In a follow-up study, it was shown that *L. reuteri*-mediated rescue of social behavior in multiple mouse models of social dysfunction requires VN integrity, as the rescue was attenuated in vagotomized mice (Sgritta et al., 2019). Furthermore, it is dependent on oxytocin receptor expression in dopaminergic neurons. Importantly, while these studies demonstrate necessity of the vagus nerve in *L. reuteri*-mediated impacts on mouse social behavior, they fall short of demonstrating sufficiency, thus leaving open the possibility of a rescue mechanism dependent on multiple axes of gut-microbiota-brain communication.

While neuroanatomic components of the gut-microbiota-brain axis are primarily involved in postnatal brain development, maternal neuroanatomic connections between the gut and the brain may also play a role, albeit indirectly, in offspring prenatal neurodevelopment. Like maternal malnutrition, alterations in maternal mental health, such as prolonged and severe stress, depression, or anxiety, have been suggested to increase the risk for neurodevelopmental and mood disorders in the offspring. Indeed, animal studies in this field (Weinstock, 2017) supported the hypothesis of a potential link between antenatal distress, dysbiosis of the maternal gut microbiome (Jasarevic et al., 2017, 2018), and long-lasting behavioral alterations in the offspring (Jasarevic and Bale, 2019).

To determine pathways by which maternal stress or mood impact fetal development, some studies have investigated the role of the hypothalamic–pituitary–adrenal (HPA) axis, an important component of the gut-microbiota-brain axis known modulate the response to psychological and physical stressors (Smith and Vale, 2006). Intriguingly, the neuroendocrine-HPA axis is modulated by the gut microbiota (Sudo, 2016). The precise mechanisms by which microorganisms living in the gut influence HPA axis activity and, more broadly, the neuroendocrine system, however, remain poorly understood. Several microbiota-derived metabolites, such as SCFAs, gastrointestinal hormones, and neurotransmitters acting together with the immune system, might exert direct modulatory effects on the HPA. Studies comparing the activity of the HPA axis in germ-free and conventionally colonized mice found elevated ACTH levels in the plasma of germ-free mice compared to controls, which was reverted after gut colonization with specific microbial strains, thus suggesting a role for microbiota in regulating the host stress response (Sudo et al., 2004). Conversely, both stress and HPA axis activity may have a role in determining gut microbiome composition (Dinan and Cryan, 2012).

Given that diet is a master regulator of gut microbiome composition, it is reasonable to hypothesize that diet-induced dysbiosis in both the maternal and offspring gut microbiome can lead to abnormal HPA axis activation and stress response, thus triggering mechanisms underlying fetal programming of disease in offspring. While dysbiosis can trigger abnormal activation of the HPA axis and immune system, pre- and probiotics have been shown to positively affect host stress and immune responses (Dinan and Cryan, 2012; Farzi et al., 2018). For instance, a combination of probiotics decreased depression-like behavior and HPA axis activation, shown as a downregulation of CRF receptor expression in the hippocampus, and changes in cytokine profiles, in HFD-fed rats (Abildgaard et al., 2017). Future studies are needed to elucidate the role of maternal diet-induced dysbiosis of the gut microbiome on the HPA axis and host stress response, and the related implications for offspring neurodevelopment.

6. Concluding perspective

Between 1961 and 1964, a systematic population health study to understand the link between maternal malnutrition and severe fetal malformations, including neural tube defects (NTDs), was undertaken in women receiving antenatal care at Mill Road Maternity Hospital in Liverpool, England (Hibbard et al., 1965). Mill Road primarily served women of low socioeconomic status with limited access to adequate nutritional requirements to support maternal and fetal health throughout pregnancy. The incredible success of advances in prenatal obstetric care in reducing perinatal mortality during the first half of the 20th century had laid bare the effects of poor maternal nutrition during pregnancy on fetal development. Infants were now surviving hard-wrought pregnancies only to be born with significant fetal malformations, such as NTDs, and folate insufficiency was a suspected culprit. In this and subsequent studies, including a large-scale randomized clinical trial undertaken by the British Medical Research Council (1991), folate supplementation was shown to significantly reduce NTD incidence. Daily supplementation with 800 μg folic acid during pregnancy reduced NTD risk by 100 % in a Hungarian study (Czeizel and Dudas, 1992). The incredible success of these efforts led to widespread, multinational adoption of government-mandated folic acid fortification of food supplies while public health organizations (including the US Centers for Disease Control) promoted folic acid supplementation for all women of childbearing age. Notably, not all pregnancies prior to widespread adoption of folic acid supplementation were high risk for NTD–on the contrary, relatively few were; however, the benefit-to-risk ratio of folic acid supplementation in women of childbearing age merited the universally-applied recommendation. In a Maslow-esque turn of fate, we may be on the precipice of realizing an analogous inflection point in antenatal care in terms of our ability reduce the impact of maternal diet-induced dysbiosis of the gut microbiome on fetal programming of disease: the prenatal probiotic.

The body of clinical and preclinical evidence we discuss in this review demonstrates that the maternal gut microbiome is a powerful regulator of fetal and early postnatal development with the potential to influence long-term health outcomes of offspring. It is also highly targetable (Jasarevic and Bale, 2019; Lam et al., 2019; Sonnenburg and Sonnenburg, 2019).

Far from standing alone, maternal periconceptual, prenatal, and postnatal supplementation with probiotics could be incorporated into a comprehensive regimen of maternal-child prophylactic care–including dietary, micronutrient supplementation, folic acid and vitamin D supplementation, and cognitive behavior approaches–to facilitate positive long-term health outcomes in the dyad. While it is logical to think that encouraging adherence to dietary guidelines alone would be a sufficient means of modifying the maternal gut microbiome during pregnancy (Cirulli et al., 2020), and, by consequence, managing gestational weight gain and helping to prevent maternal dysbiosis-associated adverse health outcomes in offspring, historical precedent suggests otherwise.

Unfortunately, adherence to self-management dietary guidelines is particularly low in women of low sociodemographic status (Carolan, 2013; Carolan et al., 2012), who are the very population hit hardest by systemic societal issues, including an increased likelihood of residing in “food deserts” and, consequently, obesity (Parisi et al., 2018; Wilcox et al., 2020). Encouragingly, while one recent trial assessing the feasibility and acceptability of a brief

weight management intervention specifically cited poor recruitment (35 % of goal) as a barrier to feasibility (Daley et al., 2020; Parretti et al., 2020), the efficacy of several app-based interventions are under active investigation (Larsen et al., 2020; Marko et al., 2016). Additionally, trials such as "Prepare" (LeBlanc et al., 2016) are underway to assess the efficacy of promoting weight loss in overweight and obese women prior to conception through face-to-face interventional programs that include monitoring and evaluating physical activity and dietary habits. That said, a recent study in which patients with irritable bowel syndrome (IBS) were randomly assigned to either a "Comprehensive Self-Management (CSM)" or control cohort reported an absence of change in the CSM group gut microbiome composition at the end of the study period (Kamp et al., 2021), suggesting that dietary changes alone may fail to substantially alter a dysbiotic gut microbiome. Analysis of cross-sectional data collected from >1300 pregnant women in the US revealed an average 77 % adherence to one or more dietary supplements during pregnancy, with 64 % of participants self-reporting use of prenatal supplements (Jun et al., 2020); however, rates among women in their first trimester, aged 20–34 years, or of lower income status were lower than the average. Prenatal probiotic supplementation will not be a panacea for preventing neurodevelopmental disorders, given the multitude of factors contributing to their etiology, nor all other disorders associated with maternal obesity; however, with the potential to enrich the diversity of the maternal gut microbiome, provide microbially-derived metabolites essential to fetal development, and dampen runaway maternal inflammation, like with folic acid supplementation, the benefits are likely to significantly outweigh the risks.

Promisingly, a randomized double-blinded Danish study investigating the efficacy of a multistrain probiotic *versus* placebo-control to positively impact blood glucose and gestational weight gain, and to reduce risk of gestational diabetes mellitus in obese pregnant women, demonstrated >80 % adherence to the probiotic regimen and an increase in alpha diversity of the probiotic group over time. In contrast, no increase in alpha diversity was observed in the placebo control group (Halkjaer et al., 2020). Such diversification of the maternal gut microbiome by a prenatal probiotic regimen may provide additional short- and long-term benefits to both maternal and offspring.

Obvious questions remain. Which probiotic strains will provide any, let alone optimal, benefit to mothers and their developing children? At what dose and in what formulation should the probiotics be delivered? Does the approach need to be personalized or can a particular cocktail of commensal microbes provide universal benefit? While these remain open questions that warrant additional research, studies in preclinical animal models are beginning to shed light on the mechanisms by which certain microbes alter brain development, function, and behavior, including social dysfunction–a common hallmark of many neurodevelopmental disorders.

Recent studies of the effects of probiotic species on offspring neurophysiology and behavior are revealing a convergence on molecular pathways and circuits implicated in neurodevelopmental disorders. First, unbiased whole genome shotgun sequencing of fecal microbiota collected from maternal HFD mouse offspring led to the identification of *L. reuteri*, probiotic strains of which are widely available, as the species most reduced in the offspring gut by maternal HFD intake (Buffington et al., 2016). Consistent with previous reports, reconstitution with *L. reuteri* increased hypothalamic oxytocin levels, restored social interaction-induced synaptic plasticity in dopaminergic neurons within the ventral tegmental area—a key brain region in the social reward circuit (Gunaydin et al., 2014; Hung et al., 2017)—and rescued social deficits in MHFD offspring. Second, in a related study, unbiased metabolomic analysis of the effects of *L. reuteri* on the fecal metabolome of the *Cntnap2* model for neurodevelopmental disorders (Penagarikano et al., 2011, 2015) revealed that *L. reuteri* treatment in this genetic model for neurodevelopmental disorders selectively rescues social dysfunction via upregulation of metabolites in the tetrahydrobiopterin (BH_4) synthesis pathway (Buffington et al., 2021). BH_4 is an essential cofactor for many important metabolic processes dysregulated in ASD, such as nitric oxide metabolism and dopamine synthesis. Intriguingly, improved social and cognitive skills have been reported following treatment with sapropterin, a synthetic form of BH_4–both controlled and open-label trials reported beneficial effects of sapropterin administration to children with ASD (Frye et al., 2013; Klaiman et al., 2013). Whether such species provide prophylactic benefits if delivered during pregnancy, however, has yet to be determined. Ultimately, regardless of the initiating insult, be it solely host genetics or environmental, therapeutic modulation of the maternal gut microbiome in the context of maternal diet-induced dysbiosis holds potential as an innovative approach to improving mental health outcomes in children.

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Declaration of Competing Interest

S.A.B. is an inventor on a patent application for use of *L. reuteri* on social behavior filed by Baylor College of Medicine. The authors declare no other competing interests.

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