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Review

The Central Nervous System and the Gut Microbiome

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Neurodevelopment is a complex process governed by both intrinsic and extrinsic signals. While historically studied by researching the brain, inputs from the periphery impact many neurological conditions. Indeed, emerging data suggest communication between the gut and the brain in anxiety, depression, cognition, and autism spectrum disorder (ASD). The development of a healthy, functional brain depends on key pre- and post-natal events that integrate environmental cues, such as molecular signals from the gut. These cues largely originate from the microbiome, the consortium of symbiotic bacteria that reside within all animals. Research over the past few years reveals that the gut microbiome plays a role in basic neurogenerative processes such as the formation of the blood-brain barrier, myelination, neurogenesis, and microglia maturation and also modulates many aspects of animal behavior. Herein, we discuss the biological intersection of neurodevelopment and the microbiome and explore the hypothesis that gut bacteria are integral contributors to development and function of the nervous system and to the balance between mental health and disease.

Introduction

The development of the mammalian brain is an intricate process that lasts through adolescence and into early adulthood in humans. Further, the process of brain development involves extraordinary, large-scale long-distance migration of cells during fetal development to specific regions or layers, as well as navigation of their processes across even longer distances (often hundreds of cell body diameters) to build the specific circuits that underlie behavior (Geschwind and Rakic, 2013; Marín and Rubenstein, 2003). The complexity and protracted pre- and post-natal time course over which these events occur makes them highly sensitive and even vulnerable to environmental factors. In fact, many of the processes governing brain development are driven by extrinsic cues and experiences that shape the developing brain through both generative and regressive events. As the gut is our largest portal to the molecular universe, various dietary components have been shown to interact directly with the developing brain and to induce functional alterations in the mature brain (Chang et al., 2009; Zeisel, 2004), and there is now mounting evidence for a role by the gut microbiome in directing and facilitating developmental processes in the brain with long term implications to health (Figure 1 and Table 1).

The mammalian microbiome consists of unique assemblages of microorganisms (i.e., bacteria, archaea, fungi, and viruses) associated with various niches in and on the body. Research in animal models and humans has inextricably linked gut bacteria to the development and function of the immune system. The presence of entire immune cell types requires the microbiome, and specific microbes have been discovered that either promote or ameliorate immunologic disorders such as type 1 diabetes, asthma, and inflammatory bowel disease (Round and Mazmanian, 2009). If the gut microbiome can so profoundly impact the immune system, why would its influence not reach the nervous system? Indeed, germ-free (GF) mice, devoid of all associated microorganisms, exhibit increased risk-taking behaviors and hyperactivity, while also displaying learning and memory deficits compared to conventional (specific-pathogen-free; SPF) mice (Clarke et al., 2013; Gareau et al., 2011; Diaz Heijtz et al., 2011; Neufeld et al., 2011) (Table 1). Further, GF mice show changes in expression of the 5-hydroxytryptamine receptor (5-HT_{1A}), neurotrophic factors (e.g., BDNF), and NMDA receptor subunits in the hippocampus (Bercik et al., 2011a; Diaz Heijtz et al., 2011; Sudo et al., 2004), while also displaying impaired blood-brain barrier function, as well as increased myelination in the prefrontal cortex (Braniste et al., 2014; Hoban et al., 2016) (Table 1 and Figure 1). There is also evidence, albeit preliminary and mostly from animal models, for a potential role for the microbiome in neuropsychiatric conditions, including depression and anxiety (Foster and McVey Neufeld, 2013), autism spectrum disorder (ASD) (Krajmalnik-Brown et al., 2015), schizophrenia (Severance et al., 2014), and even Parkinson's disease (PD) and Alzheimer's disease (AD) (Keshavarzian et al., 2015).

In this Review, we discuss the intersection between the mammalian microbiome and the brain in both humans and
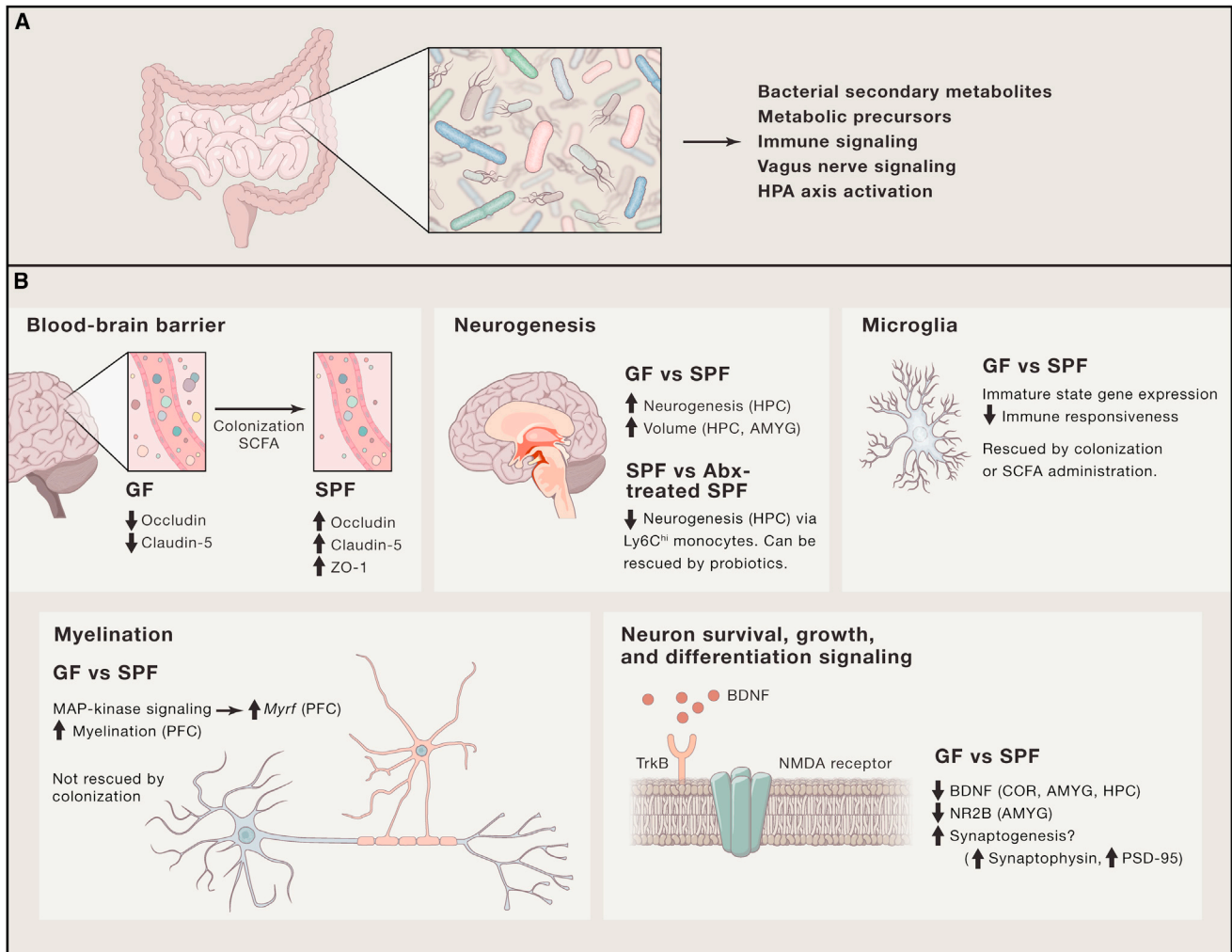
Figure 1. Intersections of Gut Microorganisms and Basic Developmental Processes
Basic developmental processes driven directly or indirectly by gut microbes and their products.
(A) Gut microorganisms relay messages to the brain via various direct and indirect mechanisms.
(B) Basic neurodevelopmental processes are modulated as a result of colonization of GF animals or depletion of gut bacteria by antibiotics. Specifically, the following processes are modulates: blood-brain barrier (BBB) formation and integrity (Braniste et al., 2014), neurogenesis (Möhle et al., 2016; Ogbonnaya et al., 2015), microglia maturation and ramification (Erny et al., 2015; Matcovitch-Natan et al., 2016), myelination (Gacias et al., 2016; Hoban et al., 2016) and expression of neurotrophins (Bercik et al., 2011a, 2011b; Desbonnet et al., 2015), neurotransmitters (Bercik et al., 2011a; O'Mahony et al., 2015), and their respective receptors.

animal models. We explore developmental trajectories and the outcomes of interactions between microbes and the brain during prenatal development, as well as postnatally and to adulthood, where microbial communities are established. Further, we highlight potential paradigms by which host-associated microorganisms may play an active role in both supporting health and potentiating disease states. By correlating microbial activities to progressive structural and functional events in the brain in mouse models and humans, we propose pathways whereby the gut microbiome may contribute to neurodevelopment and neurodegeneration. Uncovering microbial and host pathways that regulate these connections may provide novel approaches for addressing behavioral, psychiatric, and neurodegenerative disorders.

Major Processes in Neurodevelopment Coincide with Changes in the Maternal and Neonatal Gut Microbiome

Prenatal Brain Development

On the third week after conception in humans, after gastrulation is complete, neural stem cells differentiate from the epiblast, marking the first event in a sequence that would eventually result in the adult brain (Figure 2). In the cerebral cortex, which is most elaborated in humans (Geschwind and Rakic, 2013), neural progenitor cells (NPCs; also known as radial glial cells) proliferate in the ventricular zone. Committed progenitors or neurons migrate over a distance of many cell body diameters through the intermediate zone to the cortical plate, while NPCs remain in the proliferative zone (Kriegstein and Alvarez-Buylla, 2009; Rakic, 1988). While cortical neurogenesis is complete (for the most part)
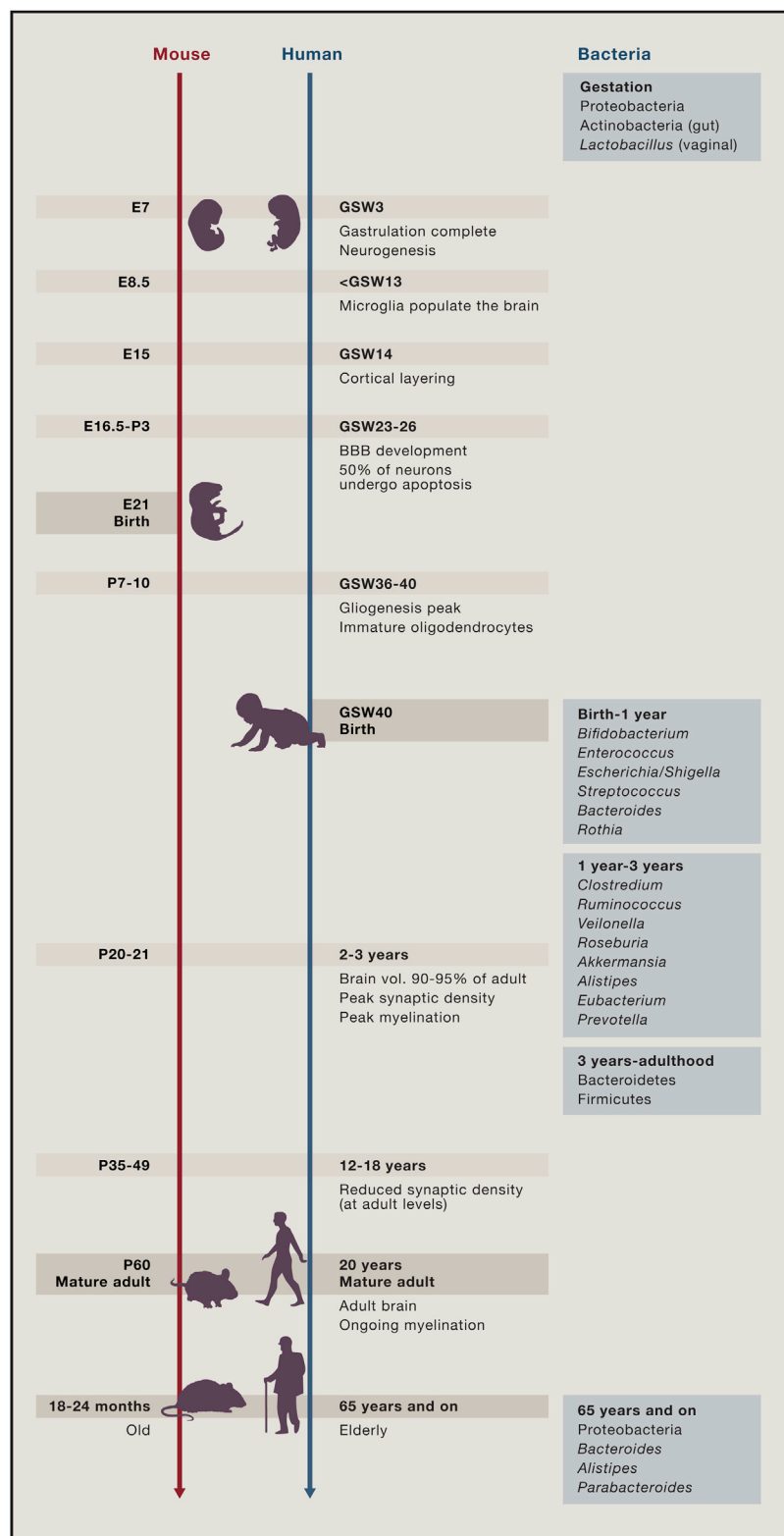
Figure 2. Major Events in Mammalian Brain Development

Developmental trajectories and key neurodevelopmental events in mice and humans (adapted from Knuesel et al., 2014; Pressler and Auvin, 2013; Semple et al., 2013). E, embryonic age; P, postnatal age; GSW, gestational week. Bacterial taxa on the right panel are the dominant ones at each life stage (Bäckhed et al., 2015; Lloyd-Price et al., 2016; Nuriel-Ohayon et al., 2016).

Mouse | **Human** | **Bacteria**

Gestation
Proteobacteria
Actinobacteria (gut)
Lactobacillus (vaginal)

E7 — GSW3
Gastrulation complete
Neurogenesis

E8.5 — <GSW13
Microglia populate the brain

E15 — GSW14
Cortical layering

E16.5-P3 — GSW23-26
BBB development
50% of neurons
undergo apoptosis

E21
Birth

P7-10 — GSW36-40
Gliogenesis peak
Immature oligodendrocytes

GSW40
Birth

Birth-1 year
Bifidobacterium
Enterococcus
Escherichia/Shigella
Streptococcus
Bacteroides
Rothia

1 year-3 years
Clostredium
Ruminococcus
Veilonella
Roseburia
Akkermansia
Alistipes
Eubacterium
Prevotella

P20-21 — 2-3 years
Brain vol. 90-95% of adult
Peak synaptic density
Peak myelination

3 years-adulthood
Bacteroidetes
Firmicutes

P35-49 — 12-18 years
Reduced synaptic density
(at adult levels)

P60
Mature adult — 20 years
Mature adult
Adult brain
Ongoing myelination

18-24 months
Old — 65 years and on
Elderly

65 years and on
Proteobacteria
Bacteroides
Alistipes
Parabacteroides

that pattern the body, and the signature of the regulatory factor gradients that govern the "Protomap" that underlies the spatial and structural differentiation of the brain are present in germinal zones of the developing embryonic brain (Marín and Rubenstein, 2003; Rakic, 1988; Stiles and Jernigan, 2010).

Following a massive neuronal expansion and migration during cortical development, ~50% of neurons undergo apoptosis during the final weeks of gestation (38—41), and only those that have been integrated into networks, and supported by neurotrophic signals, survive (Ceni et al., 2014) (Figure 2). Neurotrophins, among them brain-derived neurotrophic factor (BDNF), serve as signals for neuron survival, promote maintenance and differentiation of various cell populations (Ichim et al., 2012), and mediate various stages of neuronal circuitry establishment (Park and Poo, 2013). According to the neurotrophic hypothesis, the more connections a neuron makes, the higher the concentration of neurotrophins around it, and hence the higher chance of survival (Oppenheim, 1989). Neurogenesis is influenced by the presence of microorganisms (Figure 1). Specifically, neurogenesis in the dorsal hippocampus of adult GF mice is increased compared to conventional mice (Ogbonnaya et al., 2015). Interestingly, colonization of GF mice at weaning could not reverse this phenotype, indicating that microbial signals very early in life reduce rates of neurogenesis in the hippocampus. Moreover, adult GF mice exhibit increased volume of the amygdala and hippocampus (specifically CA2/3) and differ in dendrite morphology, while no differences in total brain volume were recorded between GF and SPF animals (Luczynski et al., 2016a). By tapping into pathways that govern neuronal differentiation and survival, via neurotrophins and their receptors, gut microbes can influence the fate of neurons in various regions of the brain and subsequently neurodevelopment and health.

by mid-gestation, gliogenesis is primarily a postnatal process. Anterior-posterior and dorsal-ventral patterning of the nervous system occurs via the same basic rules, factors, and pathways In contrast to neurons, astroglia, and oligodendrocytes, microglia are central nervous system (CNS)-resident innate immune cells derived from a primitive subset of macrophages in the

yolk sac. Although still controversial, recent reports indicate that microglia are not derived from monocytes but rather develop earlier and express distinct cell markers, different from bone-marrow-derived macrophages (specifically Ly-6C^{hi}CCR2$^+$ monocytes) that replenish the CNS following brain injury (Bennett et al., 2016; Ginhoux et al., 2010; Nayak et al., 2014; Varvel et al., 2012). In contrast, microglia were shown to originate from CD45$^-$c-kit$^+$ erythromyeloid progenitor cells and mature as CD45$^+$c-kit$^-$CX3CR1$^+$ cells in the CNS. In mice, studies show that microglia enter the brain through circulation by embryonic day 8.5 (E8.5), start expressing the microglial marker Tmem119 as early as postnatal day 6, and become fully ramified throughout the brain by postnatal day 28 (Bennett et al., 2016; Nayak et al., 2014) (Figure 2). Microglia originate from yolk-sac progenitor cells and can be replenished by bone-marrow-derived macrophages upon insult; both cell types can be subjected to microbial signals during early development (Erny et al., 2015; Khosravi et al., 2014). A central role for the microbiota in the development and maturation of the microglia has recently emerged (Erny et al., 2015; Matcovitch-Natan et al., 2016). In the absence of the microbiota, mice harbor microglia with significantly altered developmental states (Figure 1). These microglia display morphological characteristics and a gene expression profile that indicate an arrest in their developmental maturation and subsequently are maintained in an immature status (Erny et al., 2015; Matcovitch-Natan et al., 2016). Notably, microglia derived from GF mice display limited responses toward viral infection and microbially associated molecular patterns (MAMPs). Such defective responses can be rescued by administration of short-chain fatty acids (SCFAs) (Erny et al., 2015).

The blood-brain barrier (BBB) forms during gestation and serves as a selective barrier between the brain and circulation. The importance of gut microbiome and microbial metabolites in the formation of the BBB has been exemplified in GF mice (Braniste et al., 2014) (Figures 1 and 2). In the absence of gut microorganisms, the BBB is more permeable to macromolecules compared to conventionally raised animals, mediated by decreased expression of key tight-junction proteins in the brain endothelium. Furthermore, permeability decreased upon colonization of GF animals or, alternatively, upon administration of the SCFA butyrate that is produced as a result of bacterial fermentation in the gut (Braniste et al., 2014). Correspondingly, the BBB in the sterile fetus is permeable, compared to the adult BBB (Møllgård and Saunders, 1986). Recently, a lymphatic vasculature of the brain that drains from the cerebrospinal fluid in the adjacent subarachnoid space and the intrastitial fluid to the deep cervical lymph nodes was discovered (Aspelund et al., 2015). This network allows easy passage for various immune cells, as well as macromolecules and metabolites, in and out of the brain (Aspelund et al., 2015; Louveau et al., 2015). The BBB and the brain lymphatic vasculature serve as a gateway for various signals to the brain, such as circulating immune cells and soluble molecules (including hormones and neurotransmitters, both host and microbial in origin) and, along with stimulation of the vagus nerve, represent mechanisms that facilitate direct and indirect transmission of microbial signals from the gut to the brain.

The Maternal Gut and Vaginal Microbiome during Pregnancy and Its Effect on Offspring Behavior

The maternal microbiome is distinct and dynamically changing during pregnancy compared to other periods in female life (DiGiulio et al., 2015; Koren et al., 2012; MacIntyre et al., 2015; Nuriel-Ohayon et al., 2016; Romero et al., 2014a). With the progression of pregnancy, various taxa change in abundance with some becoming more dominant over others. For example, in the gut, some Proteobacteria and Actinobacteria appear to increase in relative abundance in the third trimester, compared to the first (DiGiulio et al., 2015; Koren et al., 2012) (Figure 2). The vaginal microbiome during pregnancy remains dominated by *Lactobacillus* species; however, as pregnancy progresses, the species composition varies between stable, common states termed community state types (CSTs). CSTs with higher microbial diversity in the vagina are associated with preterm birth (DiGiulio et al., 2015; Romero et al., 2014b). Some data suggest that the mammalian fetus is not necessarily sterile as commonly predicted. Studies advocate that the placenta and, at times, the amniotic fluid surrounding the fetus harbor distinct bacterial populations (Aagaard et al., 2014; DiGiulio, 2012; Kuperman and Koren, 2016; Zheng et al., 2015a); however, these findings remain controversial and require further investigation, as Lauder and colleagues (2016) demonstrated. Significant work is needed to validate and implement this information for therapeutic or diagnostic applications.

Variation in maternal microbial populations has been suggested to modulate the microbiome, neurodevelopment, and behavior of the offspring (Jašarević et al., 2015a). Perinatal administration of antibiotics can affect offspring health and immune status in both humans and mouse models (Russell et al., 2013; Stensballe et al., 2013). Administration of nonabsorbable antibiotics to rodent dams resulted in shifts of both the maternal and offspring gut microbiomes and induced hypoactivity compared to controls (Degroote et al., 2016; Tochitani et al., 2016). Moreover, offspring exhibited anxiety-like behavior and deficits in locomotion (Tochitani et al., 2016). Similarly, offspring Wistar rats exhibited reduced social behavior and increased anxiety as a result of nonabsorbable antibiotics administration to dams early in gestation (Degroote et al., 2016). A recent report indicates that maternal diet may also change both the microbial population and behavior of offspring (Buffington et al., 2016), following clinical data showing an association between maternal obesity and an ASD diagnosis in children (Krakowiak et al., 2012). A maternal high-fat diet in mice was sufficient to render offspring that are less social and exhibited repetitive behavior, as compared to controls fed normal chow. The social deficit in these mice could be reversed by administration of *Lactobacillus reuteri*, found to be missing in the gut microbiome of high-fat-diet offspring (Buffington et al., 2016). Similarly, behavioral deficits induced by antibiotic treatment during pregnancy could be rescued by cross-fostering offspring with control dams (Degroote et al., 2016; Tochitani et al., 2016). These examples indicate that maternal microbial populations can impact behavioral outcomes in the offspring. Whether these changes are mediated indirectly through effects on maternal behavior or directly alter fetal brain development remains to be determined.

While the fetal environment may or may not harbor a microbiome, the fetus is inarguably exposed to microbial products from the mother, such as secondary metabolites, fermentation products, LPS, and/or peptidoglycan (PG). Gomez de Agüero et al. (2016) elegantly demonstrated that microbial metabolites produced in the maternal gut during transient colonization of otherwise GF mice with an auxotrophic strain of *Escherichia coli* can reach the fetal compartment and induce a specific developmental program prenatally. Bacterial cell wall components can also affect offspring: PG can cross the placenta and reach the fetal brain, where it induces proliferation of neurons in the frontal cortex via increased expression of *FOXG1*, a critical regulator of forebrain development and neurogenesis. Offspring exposed to PG prenatally exhibit decreased cognitive function (Humann et al., 2016). Exposure to other microbial products prenatally and neonatally has impacts on offspring behavior. Offspring to dams exposed to propionic acid or LPS, injected subcutaneously, exhibited anxiety-like behaviors (Foley et al., 2014). These effects were observed even when offspring were exposed neonatally, suggesting a direct effect on the offspring rather than on maternal behavior (Foley et al., 2014). The maternal microbiome, the microbiome transmitted to offspring, their metabolites, and other microbial products are important in driving a developmental program in a healthy trajectory and, when perturbed, are sufficient to induce behavioral deficits in offspring.

The maternal immune system comes in close interaction with both gut microorganisms and the fetus. Immune activation during gestation has potentially severe implications on offspring physiology, neuropathology, and behavior, as well as the microbiome (reviewed by Estes and McAllister, 2016; Knuesel et al., 2014). Large-scale epidemiological studies have demonstrated that prenatal infections significantly increase the risk for schizophrenia in offspring (Khandaker et al., 2013), and data support involvement in ASD as well, although less conclusively (Gardener et al., 2011). Based on these findings, rodent models for maternal immune activation (MIA) have been developed, where prenatal administration of the Toll-like receptor ligands LPS or Poly(inosine:cytosine) as surrogates for infection induced detrimental effects on offspring neuropathology and behavior (Estes and McAllister, 2016). Furthermore, changes in offspring microbiome following MIA have been reported with implications on the metabolomic profile in the serum of these offspring (Hsiao et al., 2013). Intervention with the human commensal bacterium *Bacteroides fragilis* corrected many of the adverse effects induced by MIA (Hsiao et al., 2013). Specifically, *B. fragilis* treatment decreased intestinal barrier permeability and lowered the concentration of potentially pathogenic metabolites (Hsiao et al., 2013). Furthermore, a recent study found that MIA phenotypes depend on Th17 cells and the production of IL-17A (Choi et al., 2016). Interestingly, the development of this T helper cell was previously shown to depend on gut bacteria (Ivanov et al., 2009). MIA models demonstrate one possible axis through which the gut microbiome and immune system act in concert to shape offspring physiology, behavior, and neuropathology.

Postnatal Brain Development

Postnatal brain development is predominantly governed by synaptic development and plasticity, including the overproduction and elimination of synapses during the first decade of human life (Paolicelli et al., 2011; Zuchero and Barres, 2015). Although neurogenesis is highly limited postnatally and is confined to the subventricular zone of the lateral ventricle and the subgranular zone of the hippocampal dentate gyrus, glial cells continue proliferating, migrating, and differentiating throughout postnatal development and partially throughout life. Glial progenitors proliferate in the subventricular zone of the forebrain and migrate to various regions of the brain, where they differentiate to oligodendrocytes and astrocytes (Menn et al., 2006). Oligodendrocyte progenitor cells extend processes to neighboring axons and differentiate to oligodendrocytes and myelinate these axons, a process that extends over the first two to three decades of life in the frontal lobes of the cerebral cortex and that is crucial to development of higher cognitive function in humans (Figure 2).

Long-term antibiotic treatment of adult mice is sufficient to induce decreased neurogenesis in the hippocampus of adult mice and results in deficits in the novel object recognition task (Möhle et al., 2016). Voluntary exercise and probiotic treatment are sufficient to rescue these phenotypes (Möhle et al., 2016). Reduced numbers of $CD45^+CD11b^+Ly\text{-}6c^{hi}CCR2^+$ monocytes, but not microglia, were observed in the brains of antibiotic-treated animals. Remarkably, $CCR2^{-/-}$ knockout animals, as well as Ly-6c^{hi}-monocyte-depleted animals, show reduced hippocampal neurogenesis. Lastly, adoptive transfer of Ly-6c^{hi} monocytes into antibiotic-treated animals was sufficient to rescue the neurogenesis phenotype in the hippocampus, indicating that circulating monocytes play an important role in adult neurogenesis (Möhle et al., 2016). These reports suggest that neurogenesis, apoptosis, and synaptic pruning may be regulated by signals from the microbiome. However, more research is needed to mechanistically study the role of the microbiome in these processes in both animal models and humans. Adult neurogenesis can also be promoted by serotonin (Alenina and Klempin, 2015), and gut bacteria have been shown to play a role in serotonergic pathways both in the gut and in various regions of the brain (reviewed by O'Mahony et al., (2015).

During postnatal brain development, astrocytes and microglia are thought to facilitate pruning of weak neuronal synapses by complement activation and subsequent phagocytosis (Hong and Stevens, 2016). In the absence of microglia, for example, the adult brain harbors significantly more synapses, exemplifying that these glial cells are necessary for synaptic pruning (Paolicelli et al., 2011; Zhan et al., 2014). While complement components are secreted by multiple cells in the CNS, astrocytes and microglia are major producers of complement (Bahrini et al., 2015; Stephan et al., 2012). Microglia produce copious amounts of C1q, the first protein in the complement activation cascade, and express various complement receptors (Schafer et al., 2012; Stephan et al., 2012). Synaptic pruning, as well as other processes, shapes neuronal connections after cell differentiation and migration, refining neuronal networks following major events in postnatal brain development.

Proper conductance in neuronal axons is essential for information and signal relay, and myelination is a critical process in the development of a healthy brain that continues well into

adolescence (Davison and Dobbing, 1966). Two reports demonstrated that the presence of an intact gut microbiome modulates myelination. In these studies, myelin-related transcripts were increased in the prefrontal cortex, but not other brain regions, as a result of antibiotic-treatment (Gacias et al., 2016) or in GF mice (Hoban et al., 2016) (Figure 1). Interestingly, while antibiotic treatment was sufficient to induce elevated expression of myelin-related genes in non-obese-diabetic (NOD) mice and could be transferred by microbiome transplantation from these mice to C57BL/6 mice (Gacias et al., 2016), colonization of GF animals with SPF microbiota did not rescue the myelin phenotype (Hoban et al., 2016). These observations suggest that early-life exposure to the microbiome is necessary for dynamic response to changes in the microbiome later in life. In addition, oligodendrocyte development and differentiation rely on various signals, and among them are the chemokine CXCL1 and its receptor CXCR2. Notably, *CXCL1* expression was shown to be differentially induced in the brains of an ischemic stroke mouse model, in mice with different microbiotas, suggesting a potential role during homeostasis and development, although further investigation is needed (Benakis et al., 2016).

The Early-Life Gut Microbiome and Its Impact on Brain Development and Behavior

Under the assumption that the fetus is sterile of bacteria, the first direct encounter an infant has with the microbial world is during birth. Infants born via vaginal delivery are colonized by microbial populations that are closely related to maternal vaginal populations, dominated by *Lactobacillus* and *Prevotella* species (Dominguez-Bello et al., 2010) (Figure 2). In contrast, infants born by cesarean section (C-section) are exposed to and colonized by skin microbes such as *Staphylococcus* and *Corynebacterium* (Bäckhed et al., 2015; Dominguez-Bello et al., 2010). This initial exposure to such distinct microbial populations has various implications over the health and development of a newborn, with long-term consequences. In addition, prenatal stress changes the vaginal microbiome and has been shown to subsequently remodel the gut microbiome and metabolome of the offspring (Jašarević et al., 2015b). It has been documented that children born by C-section are at a higher risk for autoimmune diseases (Sevelsted et al., 2015). However, some restoration toward vaginal-derived microbial status can be achieved by exposing newborns to vaginal microorganisms derived from their mothers (Dominguez-Bello et al., 2016). The infant microbiome is highly sensitive to various perturbations like changes in diet and antibiotic treatment (Bäckhed et al., 2015; Koenig et al., 2011; Yassour et al., 2016). Moreover, infants are exposed to vertical acquisitions of novel microorganisms through intimate interaction with parents and siblings, as well as exposure to new environments (Bäckhed et al., 2015; Bordenstein and Theis, 2015; Rosenberg and Zilber-Rosenberg, 2016). Bäckhed et al. (2015) have identified signature taxa for various stages during the first year of life. While the newborn's gut is predominantly aerobic and inhabited by *Bifidobacterium*, *Enterococcus*, *Escherichia/Shigella*, *Streptococcus*, *Bacteroides*, and *Rothia*, gut bacterial populations are significantly closer to those of mothers, and more anaerobic, by the age of one (Figure 2). At this stage, children are already colonized with *Clostredium*, *Ruminococcus*, *Veilonella*, *Roseburia*, *Akkermansia*, *Alistipes*, *Eubacterium*,

Faecalibacterium, and *Prevotella*, in addition to other bacteria. The gut microbiome during the first 3 years of life is more amenable and prone to perturbations. Interestingly, as some bacteria can be transmitted from mother to newborn, probiotic administration to mothers during pregnancy can transfer specific species to newborns (Dotterud et al., 2015). Hence, this period of life is critical for the establishment of a healthy, stable microbiome (Lloyd-Price et al., 2016; Yatsunenko et al., 2012).

Disruption of the microbiome by administration of antibiotics or drastic changes in diet or, conversely, augmentation with probiotic microorganisms has profound effects on the microbial community and its trajectory through life. Perturbations of the microbial community may have significant impacts on the developing individual, with long-lasting effects on metabolism, physiology, and immune status, as has been suggested in animal studies (Blaser, 2016; Kuperman and Koren, 2016; Zeissig and Blumberg, 2014). Others have reported that antibiotic administration during the first year of life was correlated with depression and behavioral difficulties later in life (Slykerman et al., 2016). The administration of antibiotics pre- or postnatally changes the physiological status of the mother or its offspring in animal models and subsequently may impact the developmental trajectory of the offspring's brain or alternatively modulate behavior via primary effects on maternal behavior. Partial depletion of an animal's associated microbiota for a short period of time may not always impact behavior; a short-term treatment of rat neonates with vancomycin had no effect on anxiety- and depressive-like behaviors in adulthood. However, during adulthood, these rats showed visceral hypersensitivity, indicating that gut microbes can impact nociception (Amaral et al., 2008; O'Mahony et al., 2014). In adult mice, a 7 day course of nonabsorbable antibiotics was sufficient to decrease anxiety-like behavior. Interestingly, this effect was short lasting, and behavior normalized to baseline within 2 weeks (Bercik et al., 2011a), as the microbiome likely returned to its initial state. Long-term broad-spectrum antibiotic treatment from weaning through adulthood restructured the microbiome and subsequently modulated brain chemistry and behavior (Desbonnet et al., 2015). Correspondingly, GF animals display various behavioral and developmental phenotypes, compared to SPF animals (Arentsen et al., 2015; Bercik et al., 2011a; Desbonnet et al., 2014; Gareau et al., 2011; Diaz Heijtz et al., 2011; Luczynski et al., 2016b; Neufeld et al., 2011) (Table 1 and Figure 1). These observations indicate a close connection between the microbiome and behavior and suggest possible pathways through which they interact.

Probiotic administration augments the population with a specific microbe, either transiently or permanently, and can change the microbiome profile and function, as well as interact with the host. Probiotic bacteria have been demonstrated to alter, reverse, or prevent various conditions in mouse models and humans. In addition, experiments with reconstitution of the gut microbial population with healthy consortia by fecal microbiota transplantation (FMT) are underway (Borody and Khoruts, 2011; Hourigan and Oliva-Hemker, 2016). Beneficial bacteria were found to reduce responses to stress and anxiety, depressive-like behavior, promote social behavior, decrease repetitive behavior, and improve cognitive function and communication

in animals (Ait-Belgnaoui et al., 2012, 2014; Bercik et al., 2011b; Bravo et al., 2011; Buffington et al., 2016; Gareau et al., 2011; Hsiao et al., 2013; Sudo et al., 2004; Sun et al., 2016). This concept has been also expanded to humans where healthy volunteers that consumed a fermented milk product (containing several different probiotic bacteria) showed different brain activity during an emotional faces attention task, as measured by fMRI, in brain regions that control processing of sensation and emotion (Tillisch et al., 2013).

Mounting evidence suggests that the communication between the brain and gut microbial populations is bi-directional (Bailey et al., 2011; Carabotti et al., 2015; Moussaoui et al., 2014; Park et al., 2013). Using the maternal separation model in mice, De Palma et al. (2015) demonstrated that profound differences in the gut microbiome in response to early-life stress resulted in an anxiety-like phenotype. Moreover, gene expression in the amygdala differs between GF and SPF animals (Stilling et al., 2015). A reciprocal effect by gut bacteria has been reported as well, where specific bacteria, or complete microbial assemblages, had effects on host stress- and depression-like behaviors (Bercik et al., 2011a; Gacias et al., 2016; Sudo et al., 2004). While it is yet unclear if these examples are driven by a direct gut-brain interaction or mediated by other physiological factors induced by the disease state, these reports and others exemplify potential interactions between the microbiome, the gastrointestinal tract, and the brain.

The Adult "Steady-State" Microbiome

In adulthood, the microbiome reaches a relative equilibrium in terms of bacterial abundance and diversity and does not change significantly under stable environmental or health conditions. Known determinants that shape the microbiome are genetics (Goodrich et al., 2016), diet (Carmody et al., 2015; David et al., 2014), lifestyle (Allen et al., 2015; Kang et al., 2014), and geography (Rampelli et al., 2015; Yatsunenko et al., 2012). Health is defined rather ambiguously as "the absence of any overt disease" (Aagaard et al., 2013; Lloyd-Price et al., 2016). The healthy human microbiome was recently reviewed extensively by Lloyd-Price et al. (2016). The human microbiome is niche specific, with microbial diversity and abundance differing significantly from niche to niche. Each of these niches is colonized by specific microbial assemblages, with the phyla Bacteroidetes and Firmicutes dominating the intestine; *Streptococcus* sp. dominating the oral cavity; *Corynebacterium*, *Propionibacterium*, and *Staphylococcus* dominating the skin; and *Lactobacillus* dominating the vagina (Lloyd-Price et al., 2016) (Figure 2). Higher microbial diversity is correlated with health and functional redundancy (Lozupone et al., 2012; Moya and Ferrer, 2016). Importantly, the healthy microbiome is temporally stable, even when subjected to recurrent mild disturbances (Dethlefsen et al., 2008; Oh et al., 2016; Schloissnig et al., 2013). Decreased diversity, or lack of redundancy, in the microbiome has been reported in multiple diseases (Lloyd-Price et al., 2016).

The Microbiome in Neurodevelopmental and Mood Disorders

Neurodevelopmental disorders are classically studied from a genetic perspective (Parikshak et al., 2015; de la Torre-Ubieta et al., 2016). However, gastrointestinal comorbidities and food allergies are common in neurodevelopmental disorders, suggesting a role for the gut microbiome (de Theije et al., 2014). Thus, an appreciation for a microbial role in these conditions has been gained through profiling bacterial populations in fecal samples of patients and controls. Recent reports support the notion that the microbiome, or its disruption, can contribute to the pathology of various neurologic disorders, using mouse models and intervention studies. Evidence in rodent models suggests a direct link between the gut microbiota and stress and anxiety (reviewed by Foster and McVey Neufeld, 2013). These observations in animal models are supported by data in human subjects that associate the gut microbiome in IBD to stress disorders (Bonaz and Bernstein, 2013; Fond et al., 2014).

Autism Spectrum Disorder

The gut microbiome of autism spectrum disorder (ASD) children has been studied in multiple different cohorts using various methodologies, and a consensus between studies was rarely reported. It appears as though these small studies fail to generate a coherent picture, although differences in species richness and their diversity between ASD and controls have been repeatedly reported (De Angelis et al., 2013; Finegold et al., 2002, 2010; Kang et al., 2013; Parracho et al., 2005; Son et al., 2015; Williams et al., 2011, 2012). The gut microbiome of ASD patients have increased abundance and diversity of *Clostridia* species and a general increase in non-spore-forming anaerobes and microaerophilic bacteria compared to neurotypical controls (De Angelis et al., 2013; Finegold et al., 2002, 2010; Parracho et al., 2005). Gastrointestinal comorbidities are significantly more prevalent in children with ASD compared to controls (Mannion et al., 2013; McElhanon et al., 2014). These comorbidities often coincide with differences in the gut microbiome of these children (Son et al., 2015; Williams et al., 2011, 2012). Interestingly, *Sutterella* was found in close association with the intestinal epithelium of ASD children presenting gastrointestinal symptoms, while it was absent in controls (Williams et al., 2012). Moreover, Kang et al. (2013) reported the absence of specific probiotic members of the community such as *Prevotella* from the ASD gut bacterial population, suggesting that augmenting the microbiome with a specific microbe may be beneficial. These studies, and others, indicate a potential relationship between the microbiome (or specific microbes) and the brain in autism. Large-scale cross-center studies, using standardized methodologies, would help delineate what the significant differences are in the gut microbiome of ASD patients. Subsequent functional studies into the properties of the gut microbiome in ASD will shed light on mechanism by which the gut microbiome contributes to pathology and behavior. Understanding interactions between specific microbial species and the brain during development may help unravel the etiology of this enigmatic disorder.

Schizophrenia

To date, few studies of the schizophrenia microbiome exist. Higher incidence of lactic-acid bacteria in the oropharyngeal microbiome was reported, compared to controls (Castro-Nallar et al., 2015). Interestingly, a *Lactobacillus*-specific phage was also discovered in high abundance (Yolken et al., 2015). Another study reported a blood-specific microbiome in schizophrenia patients, compared to controls, with higher alpha and beta

diversity (Mangul et al., 2016; Severance et al., 2013). Further research in large populations is needed to show whether these differences are consistent throughout the population. Moreover, microbiomes associated with this condition should be profiled, and any potential roles in the etiology of schizophrenia should be mechanistically tested.

Depression

Evidence in rodent models suggest that the gut microbiome plays a role in depressive-like behaviors (Bravo et al., 2011; Desbonnet et al., 2010; Mello et al., 2013). Gastrointestinal symptoms are associated with depression, with ~20% of patients reporting such symptoms (Mussell et al., 2008). One hypothesis claims that depression, or subsets of this disorder, is a microglial disorder, as the onset of depression often follows intense inflammatory episodes in the brain or, conversely, decline in microglial function (Yirmiya et al., 2015). Interestingly, minocycline, a tetracycline antibacterial agent known to inhibit the activation of microglia, can diminish depressive behaviors in rodents (Molina-Hernández et al., 2008; Zheng et al., 2015b) and humans (Miyaoka et al., 2012) and has been suggested as a potent antidepressant. In light of recent evidence on the role of the microbiome in microglia maturation and activation (Erny et al., 2015; Matcovitch-Natan et al., 2016), it is compelling to speculate that the microbiome impacts depression by influencing microglial maturation and activation. It should be noted, however, that it is yet to be determined whether the antidepressive effects of minocycline are due to its antimicrobial properties, inhibition of microglial activation, or a combination of the two. Recently, Zheng et al. (2016) have shown that the beta-diversity of the gut microbiome in major depressive disorder (MDD) patients is significantly different from that of healthy controls, with significantly more Actinobacteria and less Bacteroidetes in MDD-associated microbial populations. Further, the authors transplanted human samples from MDD and control samples to GF mice and show that recipients of MDD samples exhibit depressive-like phenotypes, compared to controls (Zheng et al., 2016). These findings were reproduced by another group, where decreased bacterial richness and diversity were reported in depression, and depressive-like phenotypes could be transmitted by fecal transplantation into rats (Kelly et al., 2016). Mouse and human studies provide tantalizing suggestions that the microbiome may play an active role in driving depressive-like behaviors, suggesting potential new avenues for therapeutic development.

Neurodegeneration and the Microbiome in Old Age

Throughout aging, mammals undergo physiological changes that increase susceptibility to disease. Interestingly, the incidence of some gastrointestinal diseases increases with age (Britton and McLaughlin, 2013), and prevalence of diagnosed GI disorders is ~24% in people over 65 (Alameel et al., 2012). Notably, the enteric nervous system degenerates with age, starting in adulthood. Cholinergic nerves, as well as enteric glia cells, are lost in both the myenteric plexus and the submucosal plexus (Phillips and Powley, 2007). This degeneration is partially responsible for the increase in bowel motility symptoms prevalent in the elderly (O'Mahony et al., 2002).

The microbiome also undergoes profound remodeling in elderly populations (over 65 years old) (Biagi et al., 2012;

O'Toole and Claesson, 2010; Salazar et al., 2014) (Figure 2). Major shifts in bacterial taxa have been reported in the fecal microbiome of elderly people compared to infants and young adults, and these shifts correlate with health status and frailty in elderly people (Claesson et al., 2011; van Tongeren et al., 2005). Notably, while in adulthood Firmicutes outnumber Bacteroidetes in the gut, it appears as though the ratio shifts in favor of Bacteroidetes in the elderly (Claesson et al., 2011; Mariat et al., 2009). Specifically, Bacteroides, Alistipes, Parabacteroides, and Proteobacteria (gamma-proteobacteria, specifically) are significantly more prevalent in the elderly compared to younger adults (Claesson et al., 2011; Mariat et al., 2009) (Figure 2). Moreover, various studies show that the microbiome of elderly living in the community have a similar microbial diversity to that of younger adults than that of elderly people staying in short- or long-term care facilities (Claesson et al., 2012). Langille et al. (2014) reported that similar differences occur in older mice, compared to a younger group, and are highly correlated with mouse frailty. A clinical study testing the effects of Lactobacillus rhamnosus GG consumption in an elderly cohort found that the probiotic restructured the bacterial population toward an anti-inflammatory phenotype that favors the survival and growth of beneficial microbes and elevated SCFA production (Eloe-Fadrosh et al., 2015). The microbiome in the elderly population is significantly different from that of younger adults, is less diverse and resilient, and can be modulated by environmental factors and interventions.

Remarkably, the gut microbiome of centenarians differs significantly from that of other adults (Biagi et al., 2010, 2016). Biagi et al. (2016) found that a core gut microbiome, comprising species in the Bacteroidaceae, Lachnospiraceae, and Ruminococcaceae families, is associated with the human host throughout life, with decreasing cumulative abundance. Specifically, Coprococcus, Roseburia, and Faecalibacterium were found to be negatively correlated with age (Biagi et al., 2016). Other genera are positively correlated with age; among these are Oscillospira and Akkermansia (Biagi et al., 2016). Interestingly, certain subdominant bacterial species are enriched in centenarians, some of which are known to exert beneficial functions on their host and may play a role in maintenance of health in old age (Biagi et al., 2016). Insights into the microbiome of centenarians may unravel specific microbes with beneficial and protective effect on the host.

The Microbiome in Neurodegenerative Diseases

How initial interactions with gut microbes alter events later in life, such as during neurodegenerative diseases, is still unclear. A small number of studies to date have demonstrated different gut microbial populations in both human and animal models of neurodegenerative disease. Preliminary observations in the APP/PS1 mouse model of Alzheimer's disease (AD) indicate that these animals harbor decreased Allobaculum and Akkermansia, with an increase in Rikenellaceae compared to wild-type controls (Harach et al., 2015). Concurrently, individuals afflicted with Parkinson's disease (PD) display significantly different fecal and mucosal microbial populations (Hasegawa et al., 2015; Keshavarzian et al., 2015; Scheperjans et al., 2015). Prevotellaceae show decreased, while Lactobacilliaceae have increased, abundance compared to controls (Hasegawa

et al., 2015; Scheperjans et al., 2015). Relative levels of *Enterobacteraceae* in feces are sufficient to discriminate between specific forms of PD; patients displaying the tremor-dominant form of PD had significantly lower *Enterobacteraceae* relative abundance than those with more severe postural and gait instability (Scheperjans et al., 2015). In fact, intestinal biopsies of PD patients have indicated increased tissue-associated *E. coli* compared to healthy controls (Forsyth et al., 2011), further demonstrating the presence of an altered gut microbial community in individuals diagnosed with neurodegenerative diseases. However, this research correlating changes in the microbiome and neurodegeneration remains largely descriptive; how different microbial populations arise and their physiological consequences, if any, remain unknown.

Neuroinflammation is postulated to play a key role in the pathology of neurodegenerative diseases (Cappellano et al., 2013; Glass et al., 2010). Proinflammatory cytokines produced both in the brain and periphery modulate neuronal function and can initiate pathologic cell death (Koprich et al., 2008; McCoy and Tansey, 2008). Given the importance of microglia functions in both the prevention and promotion of neurodegenerative processes, it is tempting to speculate that the gut microbiota may influence these inflammatory diseases of the aging brain. As discussed above, bacterial fermentation products, namely SCFAs, can drive the maturation of microglia and are needed for maintenance of mature microglia (Erny et al., 2015). Interestingly, decreased SCFA concentrations in feces from PD patients, as compared to controls, were recently reported (Unger et al., 2016). Passage of MAMPs from the intestine and into the brain may produce low levels of inflammation (Pal et al., 2015). Such persistent, proinflammatory signaling has been linked to the severity of neurodegenerative disease (Cappellano et al., 2013; Glass et al., 2010). Interestingly, a recent report suggests that a physiologic role of the amyloid protein Aβ, known to form pathogenic plaques in AD, is as an antimicrobial agent to eliminate bacterial infection in the brain (Kumar et al., 2016). Studies to understand the long-term consequences of neurophysiological changes by the microbiota are critical.

While dysfunction in BBB integrity and maturation of microglia could have global effects, a recent study has revealed a specific example of neurodegenerative disease mediated by gut microbes. In a mouse model of sporadic uveitis, an inflammation of the middle layer of the eye, animals exhibit increased inflammation and loss of cells in the neuroretina leading to vision dysfunction. This inflammation is mediated by autoreactive T cells that recognize antigens present in the retina, a typically immune-privileged tissue. The activation of autoreactive T cells in these mice is dependent on the microbiota (Horai et al., 2015). In fact, not only are these T cells reactive toward retinal proteins, they are also capable of recognizing microbial antigens present in the gut (Horai et al., 2015). At this time, however, the microbial antigen driving this autoimmune neuroinflammation is unknown. Nonetheless, this observation suggests that "molecular mimicry" of host molecules present in the microbiota can trigger autoimmune responses that promote neurodegeneration. Other microbial molecules that mimic host structures have been suggested to play roles in promoting immune responses during AD and PD (Friedland, 2015; Hill and Lukiw, 2015). Therefore, one might consider the early developmental presence of certain gut microbes that produce these molecular mimics to potentially act as risk factors for specific immune and neurodegenerative diseases. However, no direct observation of this hypothesis has been reported to date, and the link between age-dependent influences to the microbiome and neuropathology is an active area of research.

Perspective

The microbiome plays a significant role in the well-being of its host. While much of the research on this topic to date has demonstrated that different bacterial populations are associated with certain clinical conditions, it is unclear for the most part whether these differences are causative, promote and/or enhance disease, or instead are a consequence of otherwise unrelated pathophysiology. Future research should tackle this challenging question in order to understand the intricate interaction between mammals (or any other host) and their associated microbial community. We must not continue exercises in simply cataloging bacterial populations. Rather, we must extend this foundational research approach to test the functional and ecological roles that a given microbial population plays, as well as decipher the physiological effects individual bacteria or consortia of bacteria have on their animal hosts. It is of importance to address questions of cause and effect: are changes in the microbiome underlying the pathophysiology or are they a result thereof? Are the effects on behavior direct or a result of other fundamental physiological changes? Are there defined microbial features that are necessary and sufficient to support proper neurodevelopment and prevent neurodegeneration? The use of animal models is a great tool for studying basic processes in health and disease. However, we must use caution in extrapolating results to the human condition and strive to use preclinical findings as one of several approaches to inform human health and disease.

While research on the gut-brain axis is still in relative infancy, certain basic rules have begun to emerge. It appears as though specific neurological pathways evolved to respond to the effect of microbial population, while others are unaffected by microbiome "instruction" and subject to purely genomic or other environmental cues. Interaction with host-associated microbial communities, either directly via microbial metabolites or indirectly by the immune, metabolic, or endocrine systems, can supply the nervous system with real-time information about the environment. These cues converge to control basic developmental processes in the brain such as barrier function, immune surveillance, and neurogenesis. The mechanistic understanding of how different microbial populations, beneficial or pathogenic, govern these and other functions related to health and disease holds promise in the diagnosis, treatment, and prevention of specific neuropathologies. Determining how a microbiome, changing with Westernization and other environmental factors, impacts a human population with growing rates of neurodevelopmental disorders and increasing life expectancy represents an urgent challenge to biomedical research and to society.

Table 1. Perturbation of the Microbiome and Microbial Products Can Affect Behavioral Outcomes in Mouse Models and Humans

Treatment/perturbation to Microbiome	Effects on Behavior	Known/Presumed Mechanism (by correlation)	Reference
Prenatal Effects			
Abx	offspring exhibited anxiety-like behavior and hypoactivity, as well as decreased sociability	dysbiotic microbiome	Tochitani et al., 2016; Degroote et al., 2016
High-fat diet	social deficit and repetitive behavior in offspring	dysbiotic microbiome; deficient VTA synaptic plasticity and oxytocin production	Buffington et al., 2016
Peptidoglycan	offspring show decreased cognitive function	TLR-2-mediated neuroprolifiration via FoxG1 induction in fetal cortex	Humann et al., 2016
Prenatal stress	change in offspring microbiome, gut, and brain metabolome	dysbiotic microbiome; altered free amino acid levels in offspring brain	Jašarević et al., 2015b
Maternal immune activation by Poly(I:C) administration	change in offspring microbiome and metabolome, increase repetitive behavior, anxiety-like behavior, social deficit, communication deficit	IL-6 and IL-17A mediated behavioral and cortical development abnormalities; dysbiotic microbiome	Smith et al., 2007; Choi et al., 2016
Propionic acid	offspring exhibited anxiety-like behavior		Foley et al., 2014
Postnatal Effects			
Perinatal Abx	visceral hypersensitivity	dysbiotic microbiome; decreased expression of various genes involved in pain perception in the lumbosacral region of the spine	O'Mahony et al., 2014
Abx (short-term)	short-term anxiolytic effect	dysbiotic microbiome; increased BDNF levels in hippocampus and decreased in the amygdala; phenotype independent of sympathetic and parasympathetic pathways	Bercik et al., 2011a
Abx (long-term)	anxiolytic effect, cognitive deficits	dysbiotic microbiome; increased tryptophan and decreased kynurenine in serum; increased noradrenaline in hippocampus and increased L-DOPA in amygdala; decreased BDNF in the hippocampus and vasopressin expression in the hypothalamus	Desbonnet et al., 2015
Germ-free animals	deficits in memory formation	decreased BDNF and c-Fos expression in the CA1 region of the hippocampus	Gareau et al., 2011
Germ-free animals	colonization of GF Swiss Webster with BALB/c microbiome increased exploratory behavior, while the reciprocal colonization of GF BALB/c mice with Swiss Webster microbiome reduced exploration	GF Swiss Webster mice colonized with Swiss Webster microbiota have higher levels of BDNF in the hippocampus, but not in the amygdala, compared to GF mice colonized with microbiota from BALB/c mice	Bercik et al., 2011a

Table 1. *Continued*

Treatment/perturbation to Microbiome	Effects on Behavior	Known/Presumed Mechanism (by correlation)	Reference
Germ-free animals	increased motor activity and reduced anxiety-like behavior compared to SPF	GF mice, compared to SPF controls, show increased turnover of noradrenaline, dopamine, and serotonin in the striatum; decreased expression of NGFI-A in the frontal cortex, BDNF in the basolateral amygdala and CA1 region of hippocampus, and dopamine D1 receptor in the dendate gyrus; differences in gene expression in hippocampus, frontal cortex, and striatum; higher expression of synaptophysin and PSD-95 (increased synaptogenesis)	Diaz Heijtz et al., 2011
Germ-free animals	reduced anxiety-like behavior	GF mice had decreased expression of NR2B in the amygdala; increased expression of BDNF and decreased expression of 5HT1A in the dentate gyrus	Neufeld et al., 2011
Germ-free animals	increased stress-induced HPA response	GF animals, compared to SPF controls, show increased levels of stress-induced acetylcholine and corticosterone (HPA-axis); decreased expression of NR-1 in the cortex, and of NR-2a in the cortex and hippocampus; BDNF levels were lower in the cortex and hippocampus	Sudo et al., 2004
Germ-free animals	reduced social behavior		Desbonnet et al., 2014
Probiotic administration	increased social behavior	decreased expression of specific BDNF transcripts in the amygdala	Arentsen et al., 2015
Probiotic administration	*Clostridium butyricum* administration restored cognitive function in mouse model for vascular dementia	restoration correlated with increased levels of the SCFA butyrate in feces and brains, and accompanied by activation of the BDNF-PI3K/Akt pathway in the hippocampus	Liu et al., 2015
Probiotic administration	*Clostridium butyricum* protected from cerebral ischemia/reperfusion injury in diabetic mice	Anti-apoptotic effects via Akt activation; restoration of bacterial diversity	Sun et al., 2016
Probiotic administration	*Lactobacillus farciminis* prevented stress-induced intestinal permeability and neuroinflammation in mice	decreased intestinal permeability that mediated the following stress-induced phenotypes: increased CRF expression in PVN; increased expression of proinflammatory cytokines in blood; and increased plasma levels of corticosterone	Ait-Belgnaoui et al., 2012
Probiotic administration	*Lactobacillus helveticus* R0052 and *Bifidobacterium longum* R0175 (Probio'Stick) protected from effects of water avoidance stress in mice and decreased intestinal barrier dysfunction	probiotic treatment attenuated plasma levels of HPA/ANS-related corticosterone, adrenaline, and noradrenaline as a result of stress induction, as well as activation of nuclei in the PVN, amygdala, CA3 of the hippocampus, and the dentate gyrus. Additionally, the expression of various genes related to synaptogenesis and microglia, among others, decreased as a result of probiotic treatment, while BDNF increased. Moreover, synaptogenesis increased in the dentate gyrus.	Ait-Belgnaoui et al., 2014

Table 1.   *Continued*

Treatment/perturbation to Microbiome	Effects on Behavior	Known/Presumed Mechanism (by correlation)	Reference
Probiotic administration	*Lactobacillus rhamnosus* (JB-1) reduced stress induced anxiety- and depression-like behaviors in mice	probiotic decreased levels of stress-induced plasma corticosterone; changed expression levels of $GABA_{B1b}$, $GABA_{A\alpha1}$, and $GABA_{A\alpha2}$ throughout the brain in a vagus-dependent manner	Bravo et al., 2011
Probiotic administration	*Lactobacillus rhamnosus* (R0011) and *Lactobacillus helveticus* (R0052) (Lacidofil) reduced anxiety-like behaviors in mice	increased BDNF and c-Fos expression in the hippocampus	Gareau et al., 2011
Probiotic administration	*Lactobacillus reuteri* corrected social deficit in mice	probiotic restored levels of oxytocin-producing cells in the PVN and synaptic plasticity in the VTA	Buffington et al., 2016
Probiotic administration	monoassociation with *Bifidobacterium infantis* reversed increased stress-induced HPA response in GF mice	treatment of GF mice with probiotic or colonizing with SPF microbiome early in development normalized levels of stress-induced acetylcholine and corticosterone; normalized expression of NR1 in the cortex, and of NR2a in the cortex and hippocampus; normalized BDNF levels in the cortex and hippocampus	Sudo et al., 2004
Probiotic administration	*Bifidobacterium longum* NCC3001 reduced colitis-induced anxiety-like behaviors in mice	probiotic decreased anxiety, but not pathology, in a vagus-dependent manner; excitability of enteric neurons incubated in probiotic-fermented media was lower than controls	Bercik et al., 2011b
Probiotic administration	fermented milk product affected brain activity in regions processing emotion and sensation in healthy human subjects	probiotic reduced activity in response to an emotional faces attention task in the insula cortex and somatosensory cortex	Tillisch et al., 2013
Probiotic administration	*Bacteroides fragilis* corrected anxiety-like and repetitive behaviors in mice	partial restoration of microbial community; restoration of intestinal barrier function	Hsiao et al., 2013

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