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The Role of the Gut Microbiome in Mediating Neurotoxic Outcomes to PCB Exposure

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Abstract

A series of complex physiological processes underlie the development of the microbiota, gut, and brain in early life, which together communicate via the microbiota-gut-brain axis to maintain health and homeostasis. Disruption of these processes can lead to dysbiosis of the microbiota, pathophysiology of the gut and behavioral deficits including depression, anxiety and cognitive deficits. Environmental exposures, particularly in early life, can interfere with development and impact these pathways. This review will focus on the role of the microbiome and the gut in neurodevelopment and neurodegeneration as well as the impacts of environmental exposures, particularly to the neurotoxicant polychlorinated biphenyls (PCBs), given that the gut serves as the primary exposure route. There exists extensive research on the importance of the microbiome in the developing brain and connections with autism spectrum disorder (ASD) and increasing links being established between the microbiome and development of Alzheimer's disease (AD) in the elderly. Finally, we will speculate on the mechanisms through which PCBs can induce dysbiosis and dysregulate physiology of the gut and brain.

INTRODUCTION

Humans are colonized with millions of microorganisms that live both inside the body and outside on the surface of the skin, with the gastrointestinal (GI) tract containing the most diverse and abundant species. Starting from birth, when colonization is initiated, the gut microbiota serves a multitude of functions ranging from maintaining metabolism to mediating protection of the host. For example, in infants the microbiota aids in the digestion and metabolism of colostrum by consuming milk oligosaccharides and in adults it aids in vitamin synthesis and production of absorbable short chain fatty acids (Jiang et al., 2018; Yang et al., 2016). The microbiome also promotes differentiation of the intestinal epithelium and allows homeostatic maintenance of the immune system (Yang et al., 2016). Dysbiosis, or disruptions in the composition of the microbiota, is associated with multiple diseases, not

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only within the GI tract, but including numerous extra-intestinal sites such as the brain, skin, lung, etc., with increasing frequency.

The GI tract is responsible for nutrient uptake and maintenance of appropriate protection from noxious antigens consumed from food and water sources, two seemingly dichotomous processes (Sharkey et al., 2018). To maintain both these critical functions, epithelial cells form a semi-permeable barrier, which begins to tighten after birth and serves to protect the host from many environmentally acquired exposures, including chemical, bacterial, and plant-based antigens after entering the oral cavity. The epithelium works in concert with the microbiota to regulate this protection. Given that the GI tract is the largest immune organ in the body and contains as many nerves as the brain, signals from the GI tract can be transmitted throughout the body, with the brain being a prominent example of recent research interest.

Together, the mammalian microbiota, gut, and brain form a complex, dynamic communication network responsible for the development, maintenance and modulation of the immune, GI, and central nervous (CNS) systems (Foster and McVey Neufeld, 2013). This network, termed the microbiota-gut-brain (MGB) axis, arises from key perinatal developmental events (Yang et al., 2016; Yang et al., 2013). Given the interlinked physiology of these systems and the proximity of their developmental timelines, it is perhaps unsurprising that the disruption of one component can skew the balance of the axis, leading to dysfunction affecting the other systems. For instance, impaired colonization of the gut microbiota during the early postnatal period may lead to dysbiosis which in turn impacts the endocrine stress axis (Sudo et al., 2004). Furthermore, perturbations in the gut microbiome in early life increases susceptibility to a number of immune-related pathologies such as inflammatory bowel disease (IBD) and asthma (Walker, 2013). Neonatal life is also a period of increased susceptibility to environmental exposures, due to the immaturity of the systems, particularly intestinal permeability and composition of the microbiota. Here, we explore the role of the gut microbiome in the etiology of neurodevelopmental and neurodegenerative disorders in the context of environmental exposures to neurotoxicants.

Host-Microbe Interactions

As described previously, the primary site of protection following oral exposures is the GI epithelial mucosal barrier, which works in concert with the microbiota to protect against unwanted antigens. While evidence supports limited microbial exposure of the fetus in the intrauterine environment, the majority of early microbial colonization occurs with (1) vaginal, skin, and fecal contact between mother and newborn at birth, (2) postnatal ingestion of maternal breast milk, and (3) the external milieu post-birth (Diaz Heijtz, 2016). Studies have found that neonatal gut microbiota composition, distribution, and maturation trajectory are therefore highly influenced by mode of delivery, feeding of breast milk versus formula, maternal diet, environmental factors and antibiotic use. For example, gut microbiome development in infants consuming formula fortified with probiotic organisms is more similar to breastfed infants, but demonstrates a less stable, uniform microbial composition (Cong et al., 2016). The prebiotic human milk oligosaccharides present in breast milk select for specific microbial communities, such as *Bacteroides* and *Bifidobacterium*, which perform

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important functions such as pathogen inhibition, mucosal barrier function, as well as modulation and stimulation of appropriate immunological and inflammatory responses in the infant (Donovan and Comstock, 2016; Underwood et al., 2015).

Over time, fluctuations in the composition and distribution of bacterial species colonizing the gut coincide with host maturation, with the microbiome shifting to a more complex and dynamic structure until it resembles adult-like configurations by three years of age (Valles et al., 2014) (Figure 1). Microbial species that promote digestive pathways strictly utilizing lactation are replaced by organisms directly involved in solid food digestion (Nuriel-Ohayon et al., 2016). The naive immune system undergoes microbial driven education and regulation, and programming of the host metabolism occurs through the influence of gut microbiota on enterohepatic gene expression (Belkaid and Hand, 2014). Additionally, children undergo a series of developmental breakthroughs as structural changes in the brain and consequent shifts in associated behavior occur between ages 3 and 4. White matter connectivity between the temporoparietal and inferior frontal regions increases along with maturation of white matter structure in the precuneus and medial prefrontal cortex - areas of the brain associated with verbal communication, social behavior, and cognitive reasoning (Grosse Wiesmann et al., 2017).

As the brain continues to develop into adulthood and beyond, the aging process is associated with concurrent changes in microbiome complexity, with decreases in diversity and overall abundance occurring in the elderly (An et al., 2018). Furthermore, lifestyle changes, including assisted living and convalescence care, are associated with additional impacts on the microbiome, including increased risk for infections including *Clostridium difficile* (Fuchs et al., 2018. Many preclinical animal studies support the concept of host-microbe interactions involved in regulation of cognitive function (Gareau et al., 2011), with modulation of the vagus nerve by bacterial metabolites, and bacterial synthesis of neuroactive peptides as common mechanisms for this regulation (Ticinesi et al., 2018). In a recent study by Corpuz *et al.* probiotic supplementation with *Lactobacillus paracasei K71* led to better cognitive performance in a mouse model of premature aging. The authors suggest that daily intake of *L. paracasei* K71 as a preventative strategy for age related cognitive decline (Corpuz et al., 2018), indicating a critical role for the microbiota in maintaining cognition. Yeasts may also be involved in regulation of cognitive function, with *Candida albicans* infection in mice shown to cause mild memory impairment, which was resolved after clearance of the infection (Jones et al., 2019; Wu et al., 2019. Yeasts have also been found in brains from Alzheimer's disease patients, suggesting their potential involvement in disease pathogenesis (Jones et al., 2019). Taken together, strong evidence suggests that host-microbial interactions are essential for maintaining health throughout our lifetimes.

While it has been understood for some time that an altered emotional state and chronic stress can impact the GI tract and consequently the composition of the gut microbiome, there is increasing evidence that the interaction of the microbiome and the CNS is bidirectional (Fulling et al., 2019; Gareau, 2016). Perturbations of the gut microbiome can lead to increased intestinal permeability and impair the function of the intestinal barrier which in turn can lead to neuro-active metabolites gaining access to areas within the CNS (Yarandi et

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al., 2016). Gut microorganisms have been demonstrated to produce neurotransmitters and neuromodulators such as short-chain fatty acids (SCFAs), histamine, serotonin, or GABA (Giau et al., 2018). Furthermore, these microorganisms can also synthesize neurotoxic metabolites such as ammonia and D-lactic acid which is associated with impaired memory in rats (Hanstock et al., 2010). Recent studies have shown that the gut microbiota is altered in Alzheimer's disease (AD) patients with many bacterial taxa such as Bacteroides, Actinobacteria, Ruminococcus, Lachnospiraceae and Selenomonadales implicated in the pathogenesis of AD. Indeed, many of these bacteria are capable of synthesizing and releasing many neurotransmitters and neuropeptides suggesting a possible involvement in the development of AD (Kawashima et al., 2007; Zhuang et al., 2018). While the volume of evidence for gut microbiome metabolites impacting neurodevelopment and neurodegeneration is growing, further research is needed in order to identify the mechanism of their actions.

Link between GI inflammation and neuroinflammation—One of the many pathways proposed to link the gut and the brain has been the immune system. Peripheral inflammation of the gut is thought to drive inflammation of the CNS. In a normal healthy intestine, a thick mucus lining and tight barrier of epithelial cells serve to confine microorganisms to the intestinal lumen. Here, these organisms help regulate homeostatic immune responses, which promote barrier integrity, tolerance of commensal microbes and maintenance of an appropriate immune response (Al-Asmakh and Hedin, 2015). However, upsetting this delicate balance can cause damage to the intestinal lining, introduction of pathogens, and elicit strong immune reactions that can ultimately alter CNS function (Houser and Tansey, 2017). Serotonin is a critical mediator of both GI function and mood/behavior and imbalances are associated with both GI disease as well as anxiety and depression (Dunn, 2006). These two psychological conditions are commonly observed in individuals with chronic intestinal inflammation such as irritable bowel syndrome (IBS) and IBD, suggesting a connection in their etiology and pathogenesis (Clarke et al., 2009; Graff et al., 2009). The effects of intestinal inflammation can be further augmented by increases in intestinal permeability. Gut permeability leads to microbial components exiting the lumen and eliciting systemic inflammation, these responses lead to further degradation of the gut barrier (Hietbrink et al., 2009). This cyclical effect termed the "leaky gut syndrome" is indicated as a contributor in many diseases of the CNS such as autism spectrum disorder (ASD), schizophrenia (Julio-Pieper et al., 2014), depression, anxiety and post-traumatic stress disorder (Shaikh et al., 2015). Indeed, increased intestinal permeability leads to elevated blood lipopolysaccharide (LPS) and peptidoglycan levels and low-grade systemic inflammation. In mouse models of IBD, the enteric nervous system (ENS) is altered, including evidence of axonal hypertrophy and neuronal cell death (Lakhan and Kirchgessner, 2010). In a mouse model of necrotizing enterocolitis, an inflammatory GI disease affecting premature infants, neuroinflammation was observed, as determined by increased microglia activation and tissue cytokines, as well as evidence of neuronal damage in discreet brain regions (Biouss et al., 2019). Taken together, while the mechanisms of GI inflammation impact on the brain are not yet fully understood an increasing body of evidence indicates that intestinal permeability and the gut microbiota have a role in the mechanisms driving neuroinflammation.

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The role of the microbiome in neuronal development

The formation and growth of neural pathways by neurogenesis in the brain involves the migration of neurons from their sites of origin to their respective permanent destinations within the CNS (Tau and Peterson, 2010). The formation of neural circuitry is highly dependent on specific genetic, biochemical, and environmental cues occurring throughout the pre- and post-natal period. From the third week of gestation leading up to the time of birth, billions of neurons and trillions of connections are generated and rearranged into simple circuits. Through use and over time, the influence of environmental cues, molecular signaling pathways, and repetitious reinforcement further interconnect these circuits to produce complex networks, which are foundational to social, emotional, and cognitive brain domains (Colon-Ramos, 2009). In addition to the myriad of molecular substrates responsible for the precise regulation of the developing neural circuitry, the formation of these brain domains is also influenced by the downstream signaling of early post-natal gut microbiota acquisition and colonization (Lebovitz et al., 2018). The gut microbiota may also impact neurovascular integrity, with dietary interventions induced by the ketogenic diet enhancing brain vascular function, increasing beneficial microbes in the gut (Ma et al., 2018), and reducing seizure susceptibility (Olson et al., 2018) thereby reducing the risk for neurodegeneration in a mouse model.

Despite the rich array of byproducts that are beneficial to the host, some detrimental pathobiont species present in the microbiome, may negatively impact neuronal development. For example, *Bacteroidetes* can also produce noxious stimuli such as amyloids, LPSs, enterotoxins, and neurotoxins (Lukiw, 2016). These stimuli can negatively impact numerous host-microbiome interactions, particularly at interfaces where barrier integrity is crucial to maintaining symbiosis, such as GI tract and blood-brain barrier (BBB) structure and integrity. An example of this is seen with *Bacteroides fragilis*, a microbe known to be important for intestinal barrier health. Despite the benefits associated with *B. fragilis*, it also releases LPS and toxins that readily disrupt intestinal barriers and can be potent proinflammatory agents when the epithelial lining of the GI tract is breached via tight junction weakening (Zakharzhevskaya et al., 2017). Successful disruption of the intestinal barrier leaves the BBB of the CNS vulnerable to microbe-derived proinflammatory toxin exposure. For this reason, detection of *B. fragilis* LPS in blood serum is evaluated clinically as an early and major indicator of systemic inflammatory disease (Wexler, 2007). Microglia, resident macrophages within the CNS, are known to be regulated by the microbiota (Cowan and Petri, 2018; Erny et al., 2015; Thion et al., 2018), both during development and throughout life maintaining both maturation and function. Their ability to regulate neurodevelopment, including neurogenesis and synaptic pruning, suggests another means via which the microbiome can regulate neuronal circuits (Cowan and Petri, 2018). Thus, the microbiome plays a beneficial role in neurogenesis but may also play a detrimental role depending on the context of disease.

The Microbiota-Gut-Brain Axis

The development of each component of the MGB axis into a fully healthy developed system is dependent on a series of cues in early life. Thus, the perinatal period represents a time of increased vulnerability to harmful stimuli that can result in dysbiosis and long-term effects

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in adulthood. Such disruptions can predispose the individual to a variety of disorders in multiple organ systems, including neural disorders (Rogers et al., 2016). Similarly, in later life, increasing associations between the gut microbiota and neurodegenerative diseases are being made.

Studies using germ free (GF) mice, raised in isolators in the complete absence of microbes, have highlighted the impact of microbes on neurodevelopment. The absence of microorganisms has been found to result in long-lasting impacts on neurogenesis, synaptogenesis, axonal and dendritic growth, and cultivation of these connections (Rogers et al., 2016). The disturbance of synaptic density can result in altered cognitive, motor, and emotional development in GF mice compared to colonized controls (Tognini, 2017). In the absence of conventional microbial colonization, altered neurotransmitter expression and gut sensory-motor functions have also been observed (Barbara et al., 2005; Clarke et al., 2013; Diaz Heijtz et al., 2011). For instance, female GF mice display upregulated hippocampal expression of brain derived neurotrophic factor (BDNF), a protein central to new neuronal and synaptic formation and thus heavily involved in regulation of cognitive and emotional behaviors. Studies on stress reactivity and anxiety-like behavior in GF mice generally model decreased anxiety, increased stress response, and heightened adrenocorticotropic hormone (ACTH) and corticosterone levels (Clarke et al., 2013; Diaz Heijtz et al., 2011; Neufeld et al., 2011). As shown by Sudo *et al*., reversibility of the exaggerated stress response can be induced in very young mice, but not in older mice, by restoring MGB axis normalization via microbial colonization during the critical period of neural sensitivity and plasticity (Friswell et al., 2010; Sudo et al., 2004).

Neurodevelopmental and Neurodegenerative Disorders and the Microbiome

A broad and diverse range of neurological differences are recognized as part of human variation. Deviations from this range, through a combination of altered social skills, repetitive behaviors, cognitive deficits, speech and nonverbal communication can result in neurodevelopmental disorders (NDD) when present in early life and neurodegenerative disorders when occurring later in life.

Autism Spectrum Disorders—ASD is an NDD resulting from a complex set of behavioral deficits that affects individuals differently and to varying degrees of severity. Signs of ASD typically appear during early childhood sometime between the first months of age to years 2 or 3, and include affected speech, social behaviors, and increased sensitivity to external stimuli (sounds, smells, tastes, textures, lights and/or colors) (Barbaro and Dissanayake, 2009). According to the 2018 Autism and Developmental Disabilities Monitoring Network (ADDM) ASD prevalence report issued by the CDC, ASD affects 1 in every 59 births in the United States (Baio et al., 2018). While the cause of the disease is the subject of much research there does appear to be both genetic and environmental factors that contribute to disease progression. Several studies have shown that early exposure to a range of environmental factors such as viruses, medications, and chemicals can affect neurobiological development, including effects relevant to ASD (Emberti Gialloreti et al., 2019). In fact, high levels of polychlorinated biphenyls (PCBs) and organochlorine

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pesticides in the serum of pregnant mothers were associated with an increased risk of ASD development in offspring (Lyall et al., 2017).

Several subtypes of ASD exist, thought to develop due to a combinations of genetic and environmental factors, and are often accompanied by other comorbidities, such as immune dysregulation (Onore et al., 2012), IBD, and diabetes (Kohane et al., 2012). Interestingly, while ASD is defined by distinct behavioral impairments, GI distress has a particularly high prevalence and strong correlation with symptom severity in individuals with ASD (Buie et al., 2010; Coury et al., 2012). Patients have been reported to suffer from alterations in GI motility, increased intestinal permeability, and have a higher prevalence of GI diseases such as IBD when compared to healthy individuals (D'Eufemia et al., 1996; de Magistris et al., 2010; Kohane et al., 2012). Evidence from several studies point to gut bacteria as a potential risk factor in ASD progression, with a number of survey studies describing altered gut microbiota composition identified in ASD individuals, particularly elevated levels of *Clostridium* species and decreased levels of *Bacteroidaceae* (Finegold et al., 2002; Parracho et al., 2005; Song et al., 2004). Oral vancomycin administration in patients resulted in short-term improvement in symptoms that was lost after antibiotic treatment, indicating a role for the gut microbiome in the development of regressive onset ASD (Sandler et al., 2000). While many studies indicate a role for the gut in ASD there is no distinct composition of the microbiota associated with ASD individuals (Fattorusso et al., 2019). A direct comparison between studies is further complicated by differing methodologies utilized between studies and the heterogeneous nature of ASD. Thus, it remains difficult to establish a causative role for the microbiota in ASD.

While our understanding of the etiology behind ASD-associated GI issues remains incomplete, the efficacy of a range of probiotic treatments for symptoms associated with psychological distress in humans has strengthened the dysbiosis link (Messaoudi et al., 2011). Many enteric microbes serve as modulators of intestinal tight junction proteins and pro-inflammatory cytokine levels. A number of animal studies have suggested that probiotic treatment in early life is of some benefit in ASD models. A murine model of maternal immune activation (MIA) has shown that the offspring of immune-activated mothers display behavioral patterns and neuropathology along with compromised GI integrity, dysbiosis of the commensal microbiota, and alterations in serum metabolites analogous to ASD in humans (Hsiao et al., 2013). Interestingly, administration of the colonic commensal bacteria *B. fragilis* (1×10^{10} CFU every other day for 6 days from weaning) positively affected tight junction protein and cytokine levels and restored intestinal membrane function in the offspring of MIA mothers. Furthermore, the most closely related phylotypes of *B. fragilis* were notably diminished in ASD children with drastically severe GI issues (Hsiao et al., 2013). Using a maternal high-fat diet (HFD) model to induce abnormal social behavior in offspring found that HFD caused changed in neurotransmission in the hypothalamus of the newborn mice and altered social behavior. The abnormal behavior in these pups was found to be reversible by co-housing “autistic pups” with pups whose mothers were fed a normal diet and could be transferred to GF pups (Buffington et al., 2016). Finally, administration of the probiotic *Lactobacillus reuteri* reversed the abnormal changes in neurotransmission and behavioral deficits in maternal HFD offspring (Buffington et al., 2016). At present, this effect has not been well studied in humans and remains an exciting new area of research in

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the treatment of ASD. A recently published pilot study in 2019 by Sanctuary *et al.* showed that combined treatment of *Bifidobacterium infantis* and bovine colostrum product saw a reduction in the frequency of some GI symptoms and aberrant behaviors in children with ASD. Some participants had reduced Interleukin-13 (IL-13) and Tumor necrosis factor alpha (TNF-α) production, which may explain the reduction of their symptoms (Sanctuary et al., 2019). While conclusions from this study are limited due to their small sample size, the data does support preclinical studies of probiotics and ASD and requires further study.

Collectively, these data suggest that ASD is as much a disease of the gut as of the brain, with dysbiosis closely associated with ASD-associated GI deficits and behavioral abnormalities.

Alzheimer's Disease—AD is a neurodegenerative disorder of unknown etiology. The pathological hallmarks of AD include extracellular β-amyloid plaques and intracellular neurofibrillary tangles. While genome-wide association studies have indicated a strong genetic component in susceptibility to AD (Lambert et al., 2013), many studies have shown that environmental factors and intestinal dysbiosis (Bostancikliogl u, 2019) are very important to disease progression.

Evidence suggests that LPS, part of the bacterial cell wall that can impact intestinal epithelial permeability, can act in similar ways on the tight junctions of the BBB and may play a role in the neuropathology of AD. While initially soluble, LPS can form large heterogeneous aggregates over time that trigger extensive host immune responses (Lukiw, 2016). LPS-induced immune activation involves a compilation of innate immune-receptors Toll-like receptor 4 (TLR4), MD-2 protein (also known as Lymphocyte Antigen 96) and other accessory proteins. The downstream inflammatory process is associated with the characteristic amyloid beta Aβ peptide-mediated amyloidosis of AD. In rodent models of AD, it's been shown that LPS-induced neuroinflammation is linked to AD-type amyloidogenic axonal pathology and dendritic degeneration, further illustrating the capacity for commensal microbiota to generate extensive LPS and functional amyloid and its similarity to CNS amyloids (Zhao et al., 2015). Given the considerable bioavailability of microbial-derived amyloid and the overlap in subcellular location and biophysical properties to CNS amyloids, host physiology is at perpetually high risk for systemic exposure to neurotoxic compounds, especially under circumstances when the barriers of GI tract and BBB of the CNS become more permeable, as seen with increasing age (Zhao et al., 2015).

Genetic risk factors, including the apolipoprotein E 4 (ApoE4) genotype, associated with amyloid plaque deposition, as well as environmental risk factors, such as air pollution and pesticides, have been identified to contribute to the etiology of AD possibly through altered gene-environment interactions. (Eid et al., 2019). Increasingly, a role for the gut microbiota in AD has also been demonstrated, with dysbiosis and altered host-microbe interactions seen in patients, promoting inflammation and leading to neurodegeneration and cognitive deficits (Franceschi et al., 2019).

Polychlorinated biphenyls (PCBs)

PCBs are persistent organic pollutants ubiquitously found in the environment. They were primarily used as coolants and insulators in capacitors and transformers before their

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manufacture was discontinued in the USA in 1977. Despite this ban issued on their production, PCBs remain an ubiquitous environmental pollutant due to their continued release as byproducts of industrial processes and from old buildings, equipment, and waste facilities and their long half-life (Fernandez-Gonzalez et al., 2011; Herrick et al., 2007; Herrick et al., 2004; Robson et al., 2010). PCB exposure has been associated with a variety of physiological impairments such as neurobehavioral abnormalities in newborns and young children. Studies have shown that prenatal exposure is associated with lower body weight (Jacobson et al., 1990) and cognitive dysfunction in children and in young mice (Parent et al., 2016). Further evidence shows that PCBs can be transmitted in breast milk from mothers with above average PCB levels in milk that breastfed for at least 1 year. The offspring from these mothers exhibited decreased levels of activity (Jacobson et al., 1990). In contrast, mice developmentally exposed to PCBs through their drinking water exhibit hyperactivity in adulthood (Branchi et al., 2005).

While several studies have identified mechanisms for PCBs and their impacts on the brain there is no single mechanism through which all PCBs elucidate their effects. For instance, the PCB mixture Aroclor 1254 was shown to significantly reduce protein and mRNA expression of the primary glial glutamate transporter GLT-1. Glutamate uptake in adult rat brains was significantly lowered by exposure to Aroclor 1254 (Struzynska et al., 2012). In contrast, PCB 11 has been shown to promote dendritic growth via a CREB-mediated mechanism in primary cortical neuron-glia co-cultures from rats. CREB signaling is crucial for neurodevelopment and perturbations in signaling are associated with neurodevelopmental disorders (Sethi et al., 2018). PCB 95 promotes dendritic growth in rodent primary neurons via calcium-dependent transcriptional mechanisms. Additional studies indicated that PCB 95 increased phosphorylation of serine 2448 of mTOR, leading to activation of mTOR. Pharmacological inhibition and siRNA knockdown of mTOR blocked PCB 95-induced dendritic growth, highlighting the role of mTOR in PCB 95-dependent neuropsychological deficits (Keil et al., 2018). Effects of PCB 95 on dendritic growth were found to be sexually dimorphic, with neurons from female mice more sensitive than those from male mice (Keil et al., 2019). While additional studies are needed to fully elucidate the mechanisms for PCB-induced neuronal damage, these studies clearly identify detrimental impacts of exposures.

In the gut, mechanisms of PCB-induced inflammation and toxicity are even less well characterized. Following oral exposure to PCB 153, mice displayed increased intestinal permeability and had increased expression of proinflammatory cytokine in intestinal epithelial cells; inhibition of NF-κB ameliorated both these effects (Phillips et al., 2018). Intestinal inflammation following exposure was associated with genotoxic damage via activation of the ATM/NEMO pathway upstream of NF-kB activation (Phillips et al., 2018). Mice exposed to PCB 126 experienced a gut microbiota population shift at the phylum and genus level to a population associated with chronic inflammation. This dysbiosis coupled with increased intestinal inflammation was similar to that seen in the PCB 153 studies.

Taken together these data suggest that PCBs modulate signaling within both neurons and epithelial cells, supporting the hypothesis that exposures may detrimentally impact the gut-brain axis.

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PCBs and the microbiota-gut-brain axis

Despite the fact that the oral route is a common route of PCB exposure, there is little research on the impact of PCBs on the gut and the microbiome and how this may impact signaling to the brain.

Microbiota-gut—There are two major phyla that represent the bacterial core of the human microbiome, *Bacteroidetes* and *Firmicutes* (Scott et al., 2017). Although *Bacteroidetes* is the larger of the two classes of obligate anaerobic gram-negative bacteria, both contribute to healthy physiology, producing essential vitamins and cofactors, and generating otherwise unavailable nutrients by processing dietary constituents. Imbalance in this ratio between *Bacteroidetes: Firmicutes* in the microbiota is associated with disease, for example obesity, with increased levels of *Firmicutes* seen in obese individuals and in mouse models compared to lean controls (Koliada et al., 2017; Turnbaugh et al., 2006). Another phylum, Proteobacteria, is typically associated with inflammation, with dysbiotic expansion seen following enteric bacterial pathogen infection (Litvak et al., 2017) in a pro-inflammatory state such as in IBD (Matsuoka and Kanai, 2015).

Exposure to PCBs has recently been associated with changes in the composition of the gut microbiota. In 2013, Choi et al demonstrated that exposure to environmentally relevant PCB congeners (PCB153,138 and 180) significantly altered the abundance of the gut microbiome, primarily reducing the levels of Proteobacteria (Choi et al., 2013). Adult mice exposed orally to dioxin-like PCB 126 displayed intestinal dysbiosis, characterized by decreased diversity and an increase in the *Bacteroidetes: Firmicutes* ratio, which was coupled with intestinal and systemic inflammation (Petriello et al., 2018). Similarly, adult mice exposed to a PCB mixture (Fox River mixture) were found to have dose dependent alterations in bile acid homeostasis, which involved the gut-liver axis and resulted in intestinal dysbiosis (Cheng et al., 2018). PCB-induced changes in bile acid homeostasis were microbiota-dependent, with absence of effects following exposure seen in GF mice (Cheng 2018). Additional studies in other species have shown that PCB exposure can also alter both the amphibian (Kohl et al., 2015) and the zebrafish microbiome (Chen et al., 2018). A recent study from our group demonstrated in a developmental model that PCBs can cause dysbiosis of the of the microbiota in juvenile mice, as well as causing intestinal pathophysiology and inflammation (Rude et al., 2019) Developmental PCB exposure caused significant defects in the epithelial lining of both ileum and colon and resulted in altered β-diversity of the gut microbiota in a neurodevelopmental disorder susceptible model (Rude et al., 2019)

PCB exposure can also impact the GI tract directly. For instance, in adult mice exposed to PCB153, an increase in intestinal permeability and inflammatory cytokine expression was observed (Phillips et al., 2018). Interestingly, inhibition of NFκB signaling ameliorated both permeability and inflammation in mice, indicating that PCB-dependent inflammation was driven by activation of the NFκB pathway (Phillips et al., 2018). Deficits in intestinal permeability are significant, as they leave the host susceptible to other non-host derived environmental stressors, with many having been identified as significant contributing factors to a variety of adverse neurodevelopmental outcomes. (Table #1)

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Brain—Exposure to environmental neurotoxicants can lead to disruption of the balance within the CNS and peripheral nervous system (PNS) (Figure 2). A study undertaken in the Great Lakes region, an area with much PCB contamination (Li et al., 2009), showed that children exposed prenatally have lower IQs than non-exposed children (Stewart et al., 2008). A diet rich in fish, which had high levels of PCB accumulation compared to other food sources in the Great Lakes area, was associated with a much higher risk for cognitive impairments (Norstrom et al., 2010). Many pre-clinical mouse studies have also demonstrated toxic effects of PCBs on the CNS and behavior. For instance, oral exposure to PCB52 or PCB180 induces alterations in the brainstem auditory evoked potentials in rats, detrimentally impacting auditory function (Lilienthal et al., 2011). In a fetal sheep model, PCB congeners were found to affect growth, adrenal development, and cortisol production (Zimmer et al., 2013). Furthermore, PCBs have been shown to increase the permeability of the BBB and the intestinal epithelial barrier (Choi et al., 2010; Seelbach et al., 2010) potentially allowing systemic access to noxious antigens. The complexity of host-microbial interactions in the gut and the increasing awareness of the consequences of disruptions of these interactions, both within and beyond the gut, suggest that oral neurotoxicant exposures during neonatal development may have significant implications for the establishment of host-microbe interactions and that this may subsequently impact neural development.

In addition to impacting neurodevelopment, PCBs are also associated with accelerating neurodegeneration. Hippocampal behavioral deficits were observed in adult rats following exposure to a commercial PCB mixture (Aroclor 1254) including cognitive and memory impairments (Selvakumar et al., 2013). The authors speculate that exposure to PCBs led to increased generation of reactive oxygen species and subsequently decreased neurotransmitter levels, which could be reversed by treatment with an anti-oxidant (Selvakumar et al., 2013).

Taken together there is emerging evidence for the impact of PCBs and other environmental pollutants on the microbiota and in turn their effects on neurodevelopment and neurodegeneration. However further studies are needed to identify their mechanism of action and develop treatment options.

CONCLUDING REMARKS

The biological and physiological processes underlying neurodevelopment in health and disease is complex. Key genetic, biochemical, and environmental events in early life stimulate the synchronous maturation of each component in the MGB axis, laying the foundation for critical programming of appropriate mammalian cognitive, emotional, and behavioral function. Proper alignment and operation of the routes of communication used by the microbiota, gut, and brain has shown to be paramount as well, with disruption of vagus nerve communication, the immune system, gut barrier function, and microbe-derived metabolite interactions resulting in deleterious effects for both host and microbiota. As discussed, external circumstances - mode of birth delivery, exposure to environmental factors, antibiotic treatment, method of nutrient administration, maternal and infant infection, stress and epigenetics - shape development in ways still incompletely understood. Evidenced by the reduced microbial diversity, concurrent GI distress and intestinal health

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issues, and relative success of nutritional and microbial-based treatments in individuals impacted by a variety of neurodevelopmental and neurodegenerative conditions, there is strong support that the gut-microbe environment and its disturbance profoundly impact central brain processes such as neurogenesis, myelination, and microglia activation, throughout an individual's lifespan. Preclinical studies conducted over the last two decades have illuminated some of the mechanisms by which the gut microbiome modulates neurodevelopment, brain function and behavior, indicating the need for a new paradigm regarding neurodiversity and mental health approaches that encompasses the vital role microbiota play. (Table #2)

In conclusion, clear evidence exists identifying the detrimental impacts of PCB exposure on the microbiota, gut and brain. Exposures, particularly during the sensitive developmental period, can lead to dysbiosis in the gut, which can contribute to altered host-microbe interactions and intestinal pathophysiology. In addition, PCBs can impact neuronal function and contribute to neurological defects and behavioral impairments. Together, this suggests an important role for PCBs to impact MGB axis signaling, and further studies are warranted to identify the precise signaling mechanisms and means by which we can beneficially regulate these effects.

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Highlights

- The microbiome regulates neurodevelopment and neurodegeneration
- PCB exposure can modulate the microbiota
- PCB-microbiome interactions may contribute to disease development

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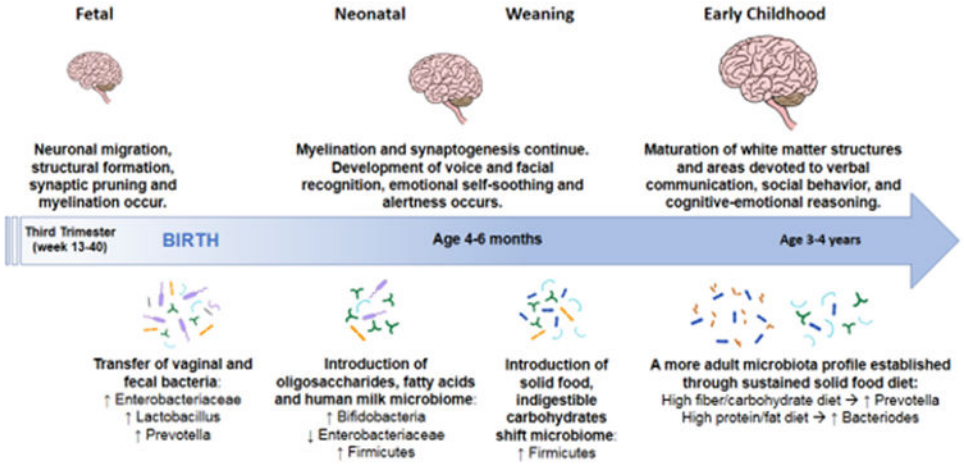

Figure 1. Alignment of developmental trajectories of the brain and the gut microbiota.

During the third trimester, neurons migrate to their designated regions of the brain, competing for limited space. Neurons that connect to their chemically defined targets receive signals that support their survival while unsuccessful neurons are eliminated through synaptic pruning. This crucial neural restructuring continues through childhood to adolescence. At the time of birth maternal transfer of fecal and vaginal bacteria occurs, initiating colonization with species such as *Enterobacteriaceae*, *Lactobacillus*, and *Prevotella*. Between the age of 4-6 months, the infant begins to acquire the ability to perceive, interpret and recognize information as well as increasing alertness and orientation to the surrounding environment. In parallel, breastfeeding introduces oligosaccharides, fatty acids and human milk microbiome, decreasing *Enterobacteriaceae* populations and favoring milk-oriented microbiota like *Bifidobacteria* and *Firmicutes*. At the time of weaning, ingestion of solid food produces another shift towards promoting growth of mature microbiota, which aid in digestion of complex carbohydrates and starches and boosts vitamin production. Around ages 3-4 years, white matter volumes continue to increase and reorganize, with the developmental changes in cortical thickness and brain volume correlating with maturation milestones of cognitive function such as verbal communication, social behavior and cognitive-emotional reasoning. A sustained, solid food diet further establishes a more complex, adult-like gut microbiota profile. Diets that tend to be higher in fiber and carbohydrates support increases in *Prevotella* populations while diets consisting of high protein and fat select for species like *Bacteroides*.

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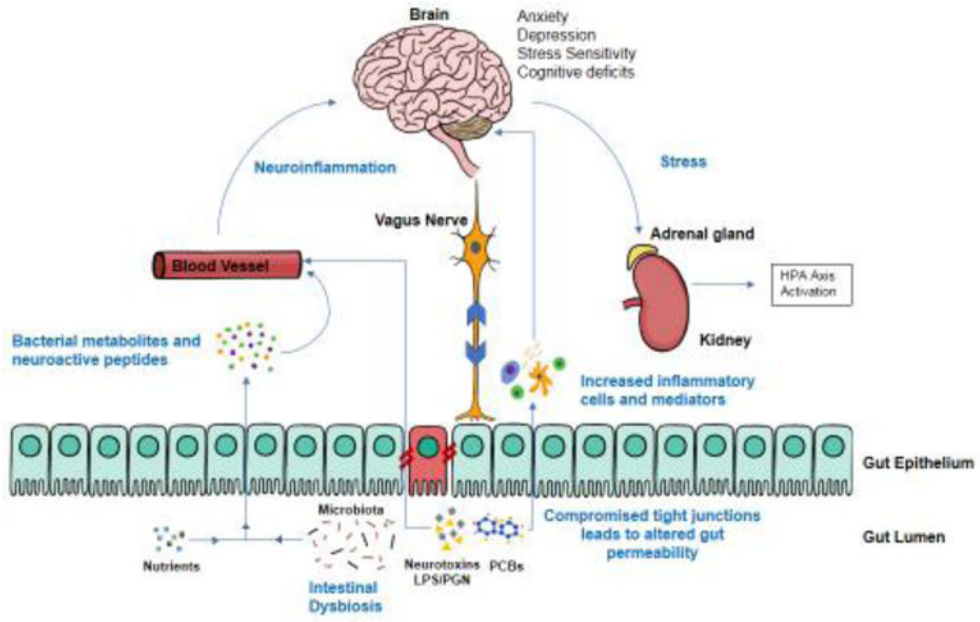

Figure 2. Downstream effects of dysbiosis on gut-brain communication.

Gut microbiota impact neurodevelopmental processes and brain function via the hormonal, immunological and neural signals which mediate the complex bidirectional communication of the MGB axis. Extrinsic innervation between the gut and the brain occurs through vagal and spinal fibers and efferent sympathetic and parasympathetic fibers extend from the brain to the gut. The brain targets specialized cells in the gut wall via specific branches of this network, including the hypothalamic pituitary adrenal (HPA) axis, which serves as the main regulator of the stress response. The host gut bacteria interface with this bidirectional communication via multiple microbial signaling pathways, aiding modulation in response to acute or chronic perturbations in homeostasis, in either the gut or the brain. Metabolites, cytokines, microbial and neurocrine signaling molecules transmit back to the brain, resulting in either transient functional alterations or longer term neuroplastic changes. Oral exposure to neurotoxicants, including PCBs, affect the establishment of host-microbe interactions, affecting neurodevelopment particularly during neonatal life. Intestinal dysbiosis impacts production of metabolites and neuroactive peptides, disrupting the communication between gut and brain and causing resulting in behavioral alterations including depression, anxiety, mood, cognition and stress sensitivity. Neurotoxicant-induced increases in intestinal permeability and inflammatory cytokine expression, can leave the host susceptible to colonization of harmful bacterial species and subsequent exposure to the pathogenic toxins they secrete. Higher levels of inflammatory cytokines due to inappropriate immune activation can result in neuroinflammation along with increased levels of brain neutrophils, as seen in neurodevelopmental disorders such as autism spectrum disorder.

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Table #1-

Summary of the neurodevelopmental and neurodegenerative impacts of PCB exposure

	PCB	Findings	Reference
Neurodevelopmental	PCB 28, 99, 118, 138/158, 153, 170, 180, 187, 194, 196/203, 199	• ↑ Risk of ASD with higher levels of PCBs	(Lyall et al., 2017)
	Aroclor 1254	• Prenatal exposure is associated with cognitive dysfunction in children and young mice • ↓ number of shaft synapses or silent synapses in newborn neurons	(Parent et al., 2016)
		Mice developmentally exposed to PCBs through drinking water exhibit: • hyperactivity in adulthood • ↑ locomotor activity and rearing levels for BDE 99 mice (hyperactivity), ↓ habituation • ↑ locomotor activity in A1254 mice compared to controls	(Branchi et al., 2005)
	PCB 11	• promotes dendritic growth via a CREB-mediated mechanism in rat primary cortical neuron-glia co-cultures.	(Sethi et al., 2018)
	PCB 95	• promotes dendritic growth in rodent primary neurons via calcium-dependent transcriptional mechanisms. • Significant ↑ in phosphorylated ser2448 mTOR in hippocampal cultures	Keil, 2018 (Keil et al., 2018)
	Environmental exposure	• Prenatal exposure associated with deficits in birth size and gestational age, postnatal growth, motor development and short-term memory loss.	(Jacobson et al., 1990)
		• ↓ in IQ by three points for every 1 ng/g of PCB exposure, which translates to ↓ in IQ by six to seven points in Full Scale IQ from least exposed group (average of 0.75ng/g) to the most highly exposed group (average of 3.15ng/g PCB)	(Stewart et al., 2008)
		• A diet rich in fish, which had high levels of PCB accumulation compared to other food sources in the Great Lakes area, was associated with a much higher risk for cognitive impairments	(Norstrom et al., 2010)
	PCB 153, 126, 118	• ↑ permeability of the BBB and the intestinal epithelial barrier • TJ proteins claudin-5, occludin, and zonula occludens-1 had altered expression	(Seelbach et al., 2010)
	PCB 52, 180	Oral exposure induces alterations in the brainstem auditory evoked potentials in rats, detrimentally impacting auditory function	(Lilienthal et al., 2011)
Neurodegeneration	Aroclor 1254	Hippocampal behavioral deficits were observed in adult rats including cognitive and memory impairments • ↑ frequency of locomotor activity, exploration and anxiety.	(Selvakumar et al., 2013)

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	PCB	Findings	Reference
		• Anxiety of the animals due to ↑ ROS	
		↓ immunoreactivity of GLT-1 transporter protein and mRNA in rat forebrain. Glutamate uptake in adult rat brains was significantly lowered	(Struzynska et al., 2012)

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Table #2:

Summary of PCB impact on microbiome and intestinal physiology

PCB	Microbiome impact	Findings	Reference
PCB 153, 138, 180	↓ Proteobacteria ↓ Bacteriodetes, ↑ Actinobacteria, ↑ Verrucomicrobia, ↑ Firmicutes.	Altered the abundance of the gut microbiome, primarily reducing the levels of Proteobacteria	(Choi et al., 2013)
PCB 126	↓ diversity ↑ Bacteroidetes:Firmicutes ratio	Intestinal and systemic inflammation • ↑ Cp1a1 expression in jejunum and colon • ↑ hepcidin in colon • ↑ TNFα in colon • ↑ occludin and Cldn3 • ↑ Muc2 expression in colon • ↓ Tlr4 in jejunum and colon • ↓ Ppard in colon • ↑ glucagon and GLP-1 in jejunum and colon	(Petriello et al., 2018)
Fox River mix (Aroclor 1248,1260,1242,1254)	↓ diversity ↓ Bacteroides	Alterations in bile acid homeostasis • ↑ Hmgcs1 • ↑ HMgcr1 • ↑ Cyp7a1 • ↑ Cyp8b1 • ↑ Cyp2c70 mRNA expression.	(Cheng et al., 2018)
PCB 126	↑ Fusobacteria in amphibians	↑ microbiota species richness and significantly enriched Fusobacteria in frogs	(Kohl et al., 2015)
MARBLES mix (PCB 28, 11, 118, 101, 153, 180, 149, 138, 84, 135, 95)	↑ Proteobacteria	intestinal pathophysiology and inflammation	(Rude et al., 2019)
PCB 153	Not reported	Significant ↑ intestinal permeability post oral administration of PCB 153 driven by activation of the NFκB pathway • ↑ il-6 • ↑ TNFα	(Phillips et al., 2018)
PCB 118, 153	Not reported	In a fetal sheep model, PCB congeners were found to affect growth, adrenal development, and cortisol production	(Zimmer et al., 2013)

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PCB	Microbiome impact	Findings	Reference
		• ↓ fetal body weight • ↓ fetal adrenal weight in the PCB 118 group • ↑ cortisol concentration in female fetuses as compared to males in the PCB 118 group	
PCB 153, 118, 104, 126	Not reported	Alterations in gut permeability via ↓ expression of tight junction proteins in vitro • ↑ NOX activity • ↓ ZO-1 • ↓ occludin NOX inhibition protected against PCB-mediated increase in epithelial permeability and alterations of ZO-1 protein expression.	(Choi et al., 2010)