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Gut microbiome: an intermediary to neurotoxicity

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Abstract

There is growing recognition that the gut microbiome is an important regulator for neurological functions. This review provides a summary on the role of gut microbiota in various neurological disorders including neurotoxicity induced by environmental stressors such as drugs, environmental contaminants, and dietary factors. We propose that the gut microbiome remotely senses and regulates CNS signaling through the following mechanisms: 1) intestinal bacteria-mediated biotransformation of neurotoxicants that alters the neuro-reactivity of the parent compounds; 2) altered production of neuro-reactive microbial metabolites following exposure to certain environmental stressors; 3) bi-directional communication within the gut-brain axis to alter the intestinal barrier integrity; and 4) regulation of mucosal immune function. Distinct microbial metabolites may enter systemic circulation and epigenetically reprogram the expression of host genes in the CNS, regulating neuroinflammation, cell survival, or cell death. We will also review the current tools for the study of the gut-brain axis and provide some suggestions to move this field forward in the future.

I. Introduction

The gut-brain axis is increasingly recognized as an important target for the health of the central nervous system (CNS) (Carabotti et al., 2015; Sharon et al., 2016; Skonieczna-Zydecka et al., 2018; Zhu et al., 2017). As a multidirectional communication network, the key components of the gut-brain axis include the CNS, the autonomic nervous system (ANS), the enteric nervous system (ENS), as well as the hypothalamic pituitary adrenal axis (HPA) (Carabotti et al., 2015). The CNS is crucial for cognitive functions including memory, social, and emotional responses, and it communicates with ANS, ENS, and HPA to orchestrate signal transduction. The ENS regulates the production of intestinal hormones and mucus secretion. In addition, the ENS and enteric immune system interact to maintain gut integrity (Yoo and Mazmanian, 2017). The ENS can polarize macrophages and put them in close proximity to extrinsic and mucosal nerve fibers (Gabanyi et al., 2016). The bioavailability of catecholamines—a sympathetic neurotransmitters and immune modulator—can be modified by gut bacteria; catecholamines are glucuronidated for excretion, whereas some gut bacteria can de-glucuronidate catecholamines and possibly affect leukocytes in the gut (Asano et al., 2012; Yoo and Mazmanian, 2017). Gut permeability and integrity can also

be regulated and monitored by the ENS through mechanoreceptors responsive to mucosal abrasions, intrinsic primary afferent neurons responsive to molecular and mechanical aberrations, and tension receptors responsive to stretch. Several compounds, including from bacteria such as short-chain fatty acids) activate receptors in neurons that regulate gut motility (Cherbut et al., 1998). The HPA modulates the release of cortisol from adrenal glands during stress response. In addition to host signaling, the gut microbiome, is important in the bidirectional communications through modulating gastrointestinal tract (GI) functions, remotely signaling to the brain and other metabolic organs, and is one of many regulatory targets of brain-to-gut signaling (Carabotti et al., 2015; Fu and Cui, 2017; Sharon et al., 2016; Skonieczna-Zydecka et al., 2018; Zhu et al., 2017).

The human microbiome dwarfs the human genome with a 10:1 ratio of nucleated cells, and 100:1 ratio of genes (Sender et al., 2016). The microorganisms in the GI tract represent the majority of the human microbiome, including bacteria, fungi, parasites, and viruses (Zhu et al., 2017). This review focuses primarily on bacteria, as they are the best characterized members of the microbiome at this time. At the phylum level, the dominant intestinal bacteria are Firmicutes and Bacteroidetes in healthy human subjects, whereas other minor phyla include Proteobacteria, Actinomycetes, Verrucomicrobia, and Fusobacteria (Eckburg et al., 2005). As illustrated in Figure 1, following exposure to environmental stressors such as environmental contaminants, drugs, dietary factors, and other xenobiotics, the gut microbiome is thought to modify the toxicological outcomes through several mechanisms. 1) Gut microbiome can directly metabolize neurotoxicants primarily through reduction and hydrolysis/de-conjugation reactions (Claus et al., 2016; Lu et al., 2015); the gut microbiome may communicate with the liver through the enterohepatic circulation of primary and secondary metabolites, altering hepatic xenobiotic biotransformation and nutrient homeostasis, which are the major functions of the liver (Klaassen and Cui, 2015; Spanogiannopoulos et al., 2016; Swanson, 2015; Visschers et al., 2013). 2) Intestinal dysbiosis as a result of chemical exposure may lead to local inflammation and gut leakiness, subsequently increasing levels of pro-inflammatory cytokines in the systemic circulation, which may contribute to neuroinflammation (Fournier et al., 2018; Janakiraman and Krishnamoorthy, 2018; Lin et al., 2018; Rea et al., 2016; Sampson et al., 2016). 3) Gut microbiota may produce neuro-reactive microbial metabolites, including short-chain fatty acids (SCFAs), ursodeoxycholic acid (UDCA), as well as various neurotransmitters such as gamma-Aminobutyric acid (GABA), histamine, acetylcholine, serotonin, melatonin, gut lumen-derived bioreactive free catecholamines, nitric oxide, and hydrogen sulfide (Asano et al., 2012; Iyer et al., 2004; Schicho et al., 2006; Sobko et al., 2006). These microbial metabolites may enter the systemic circulation and reach the molecular targets in the brain to modulate various types of cognitive functions (Carabotti et al., 2015).

In this review, we will first discuss the role of the gut microbiome in various types of neurological diseases, including Alzheimer's disease (AD) and Parkinson's disease (PD), autism spectrum disorder, attention-deficit hyperactivity disorder (ADHD), anorexia nervosa, depression, schizophrenia, bipolar disorders, as well as post-traumatic stress disorder (Table 1). We will then provide a comprehensive analysis of the literature regarding the interactions between various neurotoxicants and gut microbiome (Table 2). These neurotoxicants are selected based on research articles as well as the Casarett and Doull's

Toxicology Textbook (Klaassen CD 2013), including various drugs and environmental contaminants. While a substantial portion of the research body in this area still remains at the association level, several mechanistic studies have been performed taking advantage of novel research tools, including germ-free (GF) models, fecal/single microbial strain inoculations, anaerobic cultures, and microbial metabolite supplementations (Table 2). We will also discuss the challenges and opportunities characterizing the gut-brain axis in neurotoxicology.

II. The gut-brain axis and neurological diseases

II-1. neurodevelopmental disorders.

II-1.1. ADHD.—Attention-deficit hyperactivity disorder (ADHD) is a common condition characterized by inattention, hyperactivity, and/or impulsivity that affects 5% of children and 2.5% of adults (Faraone et al., 2015). Factors that increase the risk of ADHD include age, sex (4:1 male to female) (Faraone and Glatt, 2010), socioeconomic status (low family income) (Larsson et al., 2014), genetic variants, as well as environmental factors such as parental behavior (Harold et al., 2013; Stevens et al., 2008), prenatal metrics, and some environmental contaminants including organophosphate pesticides, polychlorinated biphenyls (PCBs), and lead (Banerjee et al., 2007; Scassellati et al., 2012). Recent studies demonstrate that the composition and predicted functions of gut microbiome are altered in ADHD patients. In one study, a decrease in parent-reported ADHD symptoms was associated with an increase in the abundance of *Faecalibacterium spp*. with no alteration in the richness of the gut microbiota (Jiang et al., 2018). A second study of male juveniles found that relative to healthy controls, subjects with ADHD had lower species richness as well as an increase in *Bacteroidaceae* (Prehn-Kristensen et al., 2018). Young adult subjects with ADHD had increased *Bifidobacterium spp*. associated with a predicted increase in cyclohexadienyl dehydratase l, which is important for the generation of the dopamine and noradrenaline precursor phenylalanine (Aarts et al., 2017). Dysregulation of dopamine and noradrenaline is implicated in ADHD etiology; however, it is unclear whether bacteria can independently induce ADHD-like behavior.

II-1.2. Autism spectrum disorder.—Autism spectrum disorder (ASD) is a severe neurodevelopmental disorder characterized by persistent social and communicative deficits as well as repetitive and restrictive patterns of behaviors, interests, and activities. It is increasingly recognized that both environmental and genetic factors play important roles in the etiology of ASD (Hallmayer et al., 2011), including the gut microbiome and ASD in children (Coretti et al., 2018; De Angelis et al., 2013; Finegold et al., 2010; Hicks et al., 2018; Kang et al., 2013; Liu et al., 2019; Pulikkan et al., 2018; Qiao et al., 2018; Rose et al., 2018; Son et al., 2015; Wang, M. et al., 2019). Interestingly, there is a high prevalence of gastrointestinal disorders in children with ASD. Gastrointestinal-related symptoms in ASD were associated with a less diverse gut microbiome and decreased abundances of the genera *Prevotella*, *Coprococcus*, and an unclassified taxon in *Veillonellaceae*, which are carbohydrate-degrading and fermenting bacteria, suggesting that carbohydrate metabolism or SCFAs may be involved in ASD (Kang et al., 2013). In ASD patients, a positive correlation was identified between high levels of the SCFA butyrate and *Faecalibacterium*

prausnitzii (Coretti et al., 2018). Male mice perinatally exposed to valproic acid to induce ASD-like behaviors also had increased caecum butyrate (de Theije et al., 2014). ASD children were found to have higher fecal abundances of *Caloramator*, *Sarcina* and *Clostridium* genera along with a decrease in *Bifidobacterium*, which is known to produce SCFAs (De Angelis et al., 2013). A similar study comparing children with ASD and neurotypical healthy controls found no differences in fecal microbiome diversity, but did identify a significant interaction between ASD and the *Cyanobacteria/Chloroplast* genus (Son et al., 2015). A comparison of Indian children with ASD relative to healthy controls identified ASD as a significant factor to explain the differences in gut phylotypes; *Lactobacillus spp*. was significantly associated with ASD using a meta-analysis of the Indian children cohort with a US cohort (Pulikkan et al., 2018). Behavioral tests and hazard models from studies investigating antibiotics or vitamin A and ASD do not support a causal relationship (Axelsson et al., 2019b; Hamad et al., 2018; Liu, J. et al., 2017). Other studies have found decreased alpha diversity and altered composition of the oral microbiome (Hicks et al., 2018; Qiao et al., 2018).

In 12 month old BTBR T + tf/J (BTBR) inbred mice, an established model of ASD for social interaction and behavior, 16 taxa were altered in a sex-specific manner relative to sex-matched C57BL/6 mice (Coretti et al., 2017). For female BTBR mice, this included an increase in *Akkermansia spp*. and a decrease in *Oscillospira spp*., whereas in male BTBR mice, there was an increase in *Lactobacillus spp*. and a decrease in *Desulfovibrio spp*. (Coretti et al., 2017). It was later shown that compared to C57BL/6J mice, adult male BTBR mice have decreased *Bifidobacterium spp*. and *Blautia spp*. associated with dysregulated bile acid and tryptophan metabolism related to ASD behavior (Golubeva et al., 2017). Male Syrian hamsters exposed to a neurotoxic dose of propionic acid exhibit ASD-like behaviors and glutamate excitotoxicity in the brain. A probiotic mixture of *Bifidobacterium breve*, *Bifidobacterium infantis*, *Lactobacillus acidophilus*, *Lactobacillus bulgaricus*, *Lactobacillus casei*, *Lactobacillus rhamnosus*, and *Streptococcus thermophiles* abrogated the ASD effects of high-dose propionic acid (El-Ansary et al., 2018). Deletion of the gene SHANK3 is associated with dysregulated neurodevelopment and autistic like behaviors (Durand et al., 2007). In Shank3 knockout mice, there was a decrease in the levels of *Lactobacillus reuteri* that correlated with decreased expression of gamma-aminobutyric acid (GABA) receptor subunits in the brain; supplementation of *L. reuteri* attenuated unsocial behavior in male Shank3 knockout mice and increased GABA receptor expression (Tabouy et al., 2018).

In summary, both ADHD and ASD patients have higher levels of *Faecalibacterium*, whereas *Bifidobacterium* is higher in ADHD but lower in ASD. Conflicting observations in the richness of gut microbiome were made in both diseases.

II-2. Neurodegenerative diseases

II-2.1. Alzheimer's disease.—

AD is a progressive degenerative neurological disorder that is among the most common causes of dementia worldwide. An estimated 5.5 million Americans are living with AD (Hebert et al., 2013). These include 5.3 million patients above 65 years of age (10% of all Americans older than 65) and 200,000 individuals below 65

(early-onset AD). More than 90% of AD cases are idiosyncratic and late-onset (after age 65).

Growing evidence supports a critical role of environmental factors interacting with genes of susceptibility to influence the initiation and progression of AD. There is an immense impetus to understand the interactions between host genes and the functional microbiome that may lead to the pathogenesis of AD (Bhattacharjee and Lukiw, 2013). In humans, gut microbiome from AD patients has decreased microbial diversity and is compositionally distinct from age- and gender-matched healthy controls, evidenced by a decrease in Firmicutes and *Bifidobacterium spp.*, but an increase in Bacteroidetes, and such dysbiosis correlated with cerebrospinal fluid biomarkers of AD (Vogt et al., 2017). In the APPS1 transgenic AD mouse model (human transgenes for both amyloid beta precursor protein [APP] and presenilin 1 [PSEN1]), GF mice had a drastic reduction of cerebral amyloid β (Aβ) pathology, a hallmark for clinical AD, whereas colonizing these GF mice with microbiota from the conventional mice increased cerebral Aβ pathology (Harach et al., 2017). Similarly, life-long combinatorial antibiotics treatment of AD mice also reduced Aβ pathology (Minter et al., 2016). Interestingly, probiotic supplementation reduced cognitive decline, accumulation of Aβ aggregates, and plasma inflammatory cytokines (Bonfili et al., 2017). Acute perinatal antibiotic-treatment resulted in long-term alterations of gut microbiota, reduction in brain Aβ deposition, and inflammatory signaling in serum and brain of aged APPS1 mice, indicating that there is a critical time window early in life to target the microbiome and modulate late-onset of AD (Minter et al., 2017).

Microbial metabolites may modulate the gut-brain axis during the pathogenesis of AD. Fecal SCFAs were decreased in AD mice (Zhang et al., 2017). In an AD mouse model, administration of butyrate, a major microbial-derived SCFA, led to epigenetic reprogramming (by inhibiting histone deacetylation [HDAC]) and improved memory, even at an advanced stage of disease progression (Govindarajan et al., 2011). Inflammation is a critical contributor to the pathogenesis of AD (Akiyama, 1994; Ardura-Fabregat et al., 2017; Eikelenboom et al., 1994), and SCFAs also have anti-inflammatory effects through HDAC inhibition (Vinolo et al., 2011). These studies suggest that SCFAs are neuroprotective. In addition to SCFAs, the microbial-derived ursodeoxycholic acid (UDCA) has been shown to be neuroprotective in various *in vitro* and *in vivo* AD models by reducing apoptosis and promoting cell survival (Ramalho et al., 2008). UDCA treatment can reduce inflammation and increase intestinal *Akkermansia muciniphila*, which is a normal gut bacterial species responsible for SCFA production (Van den Bossche et al., 2017).

In summary, gut microbiome may contribute to the pathogenesis of AD through dysbiosis-induced pro-inflammatory signaling, whereas beneficial microbial metabolites and/or bacteria that produce these metabolites may serve as novel therapeutic modalities for AD.

II-2.2. Parkinson's disease.—Parkinson's disease (PD) affects an estimated 1 million people in the US and is the second most common neurodegenerative disease; however, less than 10% of cases are considered hereditary (Nalls et al., 2014). Symptoms of PD include motor deficits (tremors), muscle rigidity, bradykinesia, and impaired gait. PD is one of a group of neurodegenerative diseases called synucleinopathies characterized by an

aggregation of α-synuclein (αSyn). Interestingly, there is a rostrocaudal gradient of αSyn in the ENS with higher expression in the upper gastrointestinal tract, and gastrointestinal symptoms often occur before motor symptoms in PD (Cersosimo et al., 2013). In a landmark study, mice overexpressing αSyn were protected from aggregation by antibiotic treatment, and exposing αSyn-overexpressing mice to microbiota of PD patients increased physical impairments compared to colonization by healthy donors (Sampson et al., 2016). In an effort to identify microbial metabolites that may antagonize PD development, Sampson et al. (2016) demonstrated that oral exposure to high concentrations of SCFAs (propionate, acetate, and butyrate) was sufficient to produce the motor deficits similar to PD in mice (Sampson et al., 2016). A human study, however, found decreased SCFAs in PD patients compared to healthy controls (Unger et al., 2016). Gut dybsiosis in PD patients included increased *Proteus spp.*, *Bilophila spp.*, and *Roseburia spp.* along with decreased *Lachnospiraceae*, *Rikenellaceae*, *Peptostreptococcaceae*, and *Butyricicoccus spp.* (Sampson et al., 2016). A cross-sectional study comparing PD patients to healthy controls found increased *Ruminococcaceae* to be associated with disease duration (Hill-Burns et al., 2017).

In summary, for AD and PD, fecal SFCAs were lower, suggesting that this class of microbial metabolites may be beneficial to prevent the disease onset. In mouse models, SCFA supplementation improved memory likely due to the HDAC inhibitor and anti-inflammation properties; however, conflicting results were observed in PD mouse models, because oral exposure to high concentrations of SCFAs actually produced motor deficit similar to PD.

II-3. Psychiatric disorders.

II-3.1. Depression.—Major depressive disorder (MDD) is a common, life-disrupting mental health disorder that is a leading cause of disability worldwide (Moussavi et al., 2007). Diagnosed by at least two weeks of low mood, MDD is accompanied by low self-esteem, loss of interest, and low energy. Environmental factors are associated with MDD, and several human studies have examined the association between gut microbiome and patients with MDD (Aizawa et al., 2016; Chen, Z. et al., 2018; Jiang et al., 2015; Lurie et al., 2015; Naseribafrouei et al., 2014). Of note, *Oscilibacter spp.* and *Alistipes spp.* showed a high association with MDD (Naseribafrouei et al., 2014). A second study also found increased *Alistipes spp.* and *Enterobacteriaceae*, as well as decreased *Faecalibacterium spp.* (Jiang et al., 2015). *Bifidobacterium spp.* and *Lactobacillus spp.* were decreased in another MDD cohort (Aizawa et al., 2016), and increased Actinobacteria and decreased Bacteroidetes were identified in female MDD patients (Chen, Z. et al., 2018). In the chronic variable stress rat model for depression, the genera *Candidatus Arthromitus* and *Oscillibacter* were increased and *Marvinbryantia, Corynebacterium, Psychrobacter, Christensenella, Lactobacillus, Peptostreptococcaceae incertae sedis, Anaerovorax, Clostridiales incertae sedis and Coprococcus* were decreased in depressed rats compared to control rats (Yu et al., 2017). The Flinders sensitive rat line—a strain used for depression studies—had decreased sample richness (alpha diversity) compared to controls with increased *Proteobacteria* and decreased *Elusimicrobia* and *Saccharibacteria* (Tillmann et al., 2018). Interestingly, transplantation of fecal microbiota from human MDD patients to microbiota-depleted rats or mice induced depression-like behaviors, such as anhedonia and anxiety (Kelly et al., 2016; Zheng et al., 2016). The transplantation of fecal microbiota from

depressed patients to GF mice suggested that the gut microbiota could disrupt CAMP Responsive Element Binding Protein 1 (CREB) signaling by down-regulating calcium voltage-gated channel subunit alpha1 E (CACNA1E) and disrupting axonogenesis of the olfactory bulb (Huang et al., 2019). Clinical trials of patients with MDD and one of three probiotics improved cognitive performance. Treatment with *Lactobacillus plantarum* 299v decreased the concentration of kynurenine, suggesting that microbial tryptophan metabolism may be important for MDD's etiology (Kazemi et al., 2018; Rudzki et al., 2019). In a male C57BL/6 mouse model for chronic unpredictable mild stress-induced (CUMS) depression, *Clostridium butyricum* treatment improved depressive behaviors, possibly because *C. butyricum* upregulated glucagon-like peptide-1 (GLP-1) in the intestine, activated GLP-1R in the brain and increased cerebral serotonin (Sun, J. et al., 2018). Overall, gut dysbiosis may contribute to MDD and supplementation of probiotics may alleviate the disorder.

II-3.2. Bipolar affective disorder and schizophrenia.—Bipolar affective disorder (BD) is a spectrum of psychiatric syndromes through a cyclical pattern of excitement and depressive behavior (Akiskal et al., 2000; Dacquino et al., 2015). BD is a major cause of global disability and premature mortality (Painold et al., 2018). Several human studies have investigated the association between the gut microbiome and BD. A relatively small cross-sectional comparison of fecal microbiome revealed a negative correlation between duration of BD and sample richness (Painold et al., 2018), and decreased microbiome richness was also observed in a monozygotic twin study comparing the risk of developing or having BD (Vinberg et al., 2019). The abundance of *Faecalibacterium spp*. was decreased in a small cohort of BD patients (Painold et al., 2018), and this was replicated in a larger cohort of BD patients that also showed a positive correlation between *Faecalibacterium spp*. abundance and better self-reported outcomes (Flowers et al., 2017). The use of atypical antipsychotics as a treatment for BD increased *Lachnospiraceae* and decreased *Akkermansia spp*. and *Sutterela spp*. (Flowers et al., 2017). Of clinical interest, patients diagnosed with BD and given the probiotic OMNi-BiOTiC® Stress Repair (*Bifidobacterium bifidum* W23, *B. lactis* W51, *B. lactis* W52, *Lactobacillus acidophilus* W22, *L. casei* W56, *L. paracasei* W20, *L. plantarum* W62, *L. salivarius* W24, *Lactococcus lactis* W19) had significant improvement in attention and psychomotor processing speed after taking the probiotic for 1 to 3 months (Painold et al., 2018).

Schizophrenia is a debilitating chronic mental health disorder characterized by delusional thoughts, disorganized behavior, and decreased participation in daily activities. Schizophrenia has increased mortality (Saha et al., 2007) and creates a heavy financial burden (Knapp et al., 2004). Although the etiology of schizophrenia is not well understood, risk factors include genetic inheritance (Schizophrenia Psychiatric Genome-Wide Association Study, 2011) and environmental interactions (Severance et al., 2015; van Os et al., 2010). Both microbial richness index (Chao) and diversity index (Shannon) were lower in patients with schizophrenia compared to healthy controls (Zheng et al., 2019). GF mice given human microbiome fecal transplants of people with schizophrenia exhibited schizophrenic-like behaviors and displayed similar glutamatergic hypofunction as other mouse schizophrenic models, which have decreased glutamate and increased glutamine and GABA (Zheng et al., 2019). A metagenomics analysis of the oropharyngeal microbiome

comparing 16 schizophrenia patients with 16 controls demonstrated increased *Lactobacillus spp*. and *Bifidobacterium spp*., as well as an increase in the fungal phylum Ascomycota (Castro-Nallar et al., 2015). Of note, a single-arm study treating schizophrenia patients with the probiotic *Bifidobacterium breve* A-1 had improved anxiety and depression scores, and they reported fewer negative symptoms (Okubo et al., 2019). *Bifidobacterium spp*. was increased in the fecal microbiota of older schizophrenic subjects given 4^{G}-β-D-galactosylsucrose as a prebiotic treatment for underweight patients (Nagamine et al., 2018).

A 16S rDNA gene sequencing study of the fecal microbiome found increased relative abundance of the genera *Succinivibrio*, *Megasphaera*, *Collinsella*, *Clostridium*, *Klebsiella* and *Methanobrevibacter* in schizophrenia patients compared to healthy controls, whereas the abundance of *Blautia*, *Coprococcus*, *Roseburia* was decreased (Shen et al., 2018). A second group found increased *Anaerococcus* whereas *Haemophilus*, *Sutterella*, and *Clostridium* were decreased; there was also an association between worsening depressive symptoms and the abundance of *Bacteroides* (Nguyen et al., 2019). Interestingly, metatranscriptomics of whole blood from healthy individuals compared to schizophrenia patients found increased microbial sample richness; increased diversity was inversely associated with CD8+ CD28− CD45RA−, indicating an association between the microbiome, immunity, and schizophrenia (Olde Loohuis et al., 2018). A schizophrenia model in rats using social isolation had increased Actinobacteria and decreased Clostridia compared to controls and also noted associations between gut microbiota and hippocampal interleukin (IL)-6 and IL-10 (Dunphy-Doherty et al., 2018).

In summary, among the 3 types of psychiatric disorders, decreased gut microbiome richness appeared to be a common feature. Faecalibacterium was decreased in both depression and BD; whereas Lactobacillus supplementation was beneficial to improve both depression and BD. Depression and schizophrenia appeared to have opposite microbial patterns: for example, depression has lower Bifidobacterium and Lactobacillus, whereas schizophrenia has higher levels of these bacteria.

II-4. Other neurological disorders associated with stress

II-4.1. Postpartum depression.—Postpartum depression is a clinically diagnosed form of MDD with onset during the peripartum period; several risk factors for postpartum depression include history of depression, pregnancy and birth complications, and psychoneuroimmune dysregulation (Association, 2013; Corwin et al., 2015; Dunn et al., 2015; Osborne and Monk, 2013). As many as 19.2% of women have a major depressive episode within the first three months postpartum (Gavin et al., 2005). Remarkably, antibiotic exposure was identified as an independent risk factor up to 2 months postpartum (Murphy et al., 2018). A cohort of 380 women in New Zealand were given the probiotic *Lactobacillus rhamnosus* HN001 or a placebo from 14–16 weeks gestation through 6 months postpartum; women given the probiotic reported lower depression and anxiety scores during the postpartum period (Slykerman et al., 2017). Dysbiosis may increase the risk of postpartum depression, whereas probiotic supplementation may decrease the risk of depressive episodes.

II-4.2. Post-traumatic stress disorder.—Post-traumatic stress disorder (PTSD) is a commonly occurring condition manifesting after exposure to trauma, such as war, sexual assault, and other distressing experiences, and has a high rate of psychiatric comorbidity (Kessler, 2000). PTSD can often occur for many years and is frequently associated with exposure to multiple traumas (Hemmings et al., 2017). In a mouse model of PTSD, in which adult male C57BL/6J mice were exposed to extreme aggression by SJL albino male mice, the microbial-influenced metabolites 3-phenylpropionate, hippurate, and phenylpropionylglycine were increased in PTSD mice (Gautam et al., 2015), indicating an altered gut microbiome. A follow-up study using the same PTSD aggressive mouse model showed an immediate and inconsistent dysregulation of microbiome composition, specifically for *Akkermansia spp*, *Anaeroplasma spp.*, *Lactobacillus spp.*, and *Oscillospira spp*. (Gautam et al., 2018). In a preliminary human study investigating the fecal microbiome in South African PTSD-affected individuals, there was no difference in the diversity of the microbiota, but there was a decrease in the total abundance of the phyla Actinobacteria, Lentisphaerae, and Verrucomicrobia associated with PTSD (Hemmings et al., 2017).

II-4.3. Anorexia nervosa.—Anorexia nervosa is an eating disorder characterized by severe weight loss (lack of appropriate weight gain or maintenance) often caused by the limitation of calories, fear of gaining weight, and denial of being underweight (Miller and Golden, 2010). Anorexia nervosa is more likely to affect females than males (Herpertz-Dahlmann, 2009). The fecal microbiota of 16 female patients showed increased sample richness at the time of admission compared to discharge (Kleiman et al., 2015). Relative to controls, samples from anorexic patients during admission were higher in the genera A*naerostipes* and *Faecalibacterium*, but an undefined genus in the family *Coribacteriales* was lower (Kleiman et al., 2015). Another study identified decreased *Clostridium coccoides*, *Clostridium leptum*, and *Bacteroides fragilis*, as well as decreased SCFAs acetic acid and propionic acid, in the stool of female patients with anorexia nervosa compared to healthy controls (Morita et al., 2015). In another cohort of anorexia nervosa patients, propionate and butyrate were decreased, corresponding to increased *Enterobacteriaceae* and *Methanobrevibacter smithii* and decreased *Roseburia spp.*, *Ruminococcus spp.*, and *Clostridium spp*. (Borgo et al., 2017). Anorexia nervosa patients who gained weight had increased sample richness; the genera in *Clostridium XI* and *Bacteroidetes* were unique to anorexia nervosa patients before weight gain (Mack et al., 2016). In BALB/c mice, a chronic caloric restriction study was conducted to determine the effect on gut microbiota (Chen et al., 2016). Briefly, caloric intake was limited to prevent weight gain starting at 28 days of age and restored to *ad libitum* feeding after day 97 until day 120 when the tissues were collected. Interestingly, the changes in gut microbiome persisted even after lifting the caloric restriction. Collectively, it is unclear if the compositional changes mechanistically contribute to anorexia nervosa.

III. Gut microbiome mechanistically contributes to behavior changes – lessons learned from germ free (GF) research models.

Studies have established the association between intestinal dysbiosis and neurological disorders of various etiologies (Alam et al., 2017; Bourassa et al., 2016; Galland, 2014;

Heiss and Olofsson, 2019; Kelly et al., 2017; McKay et al., 2017; Moos et al., 2016; Tremlett et al., 2017; Zhu et al., 2017), but the role of the gut microbiome in modulating various behavior changes requires mechanistic investigations using laboratory models such as GF rats and mice. GF rats had exacerbated neuroendocrine and behavior responses to acute stress, coinciding with alterations of the dopaminerigic turnover rate in the upper structures of the brain known to regulate stress response and anxiety-like behavior (Crumeyrolle-Arias et al., 2014). The GF rats also had higher serum corticosterone levels and elevated mRNA of corticotropin releasing factor but reduced mRNA of glucocorticoid receptor in hippocampus (Crumeyrolle-Arias et al., 2014). Similarly, GF mice had impaired cognitive behaviors in response to novel objects, corresponding to decreased expression of genes involved in brain-derived neurotrophic factor (BDNF) signaling in amygdala, which is a key region for the social brain network (Arentsen et al., 2015). In response to restraint stress, plasma levels of adrenocorticotropic hormone (ATCH) and corticosterone were also substantially higher in GF mice (Sudo et al., 2004). Conversely, under basal conditions (i.e. without an environmental stimulus), GF mice exhibited anxiolytic behavior accompanied by decreased mRNA expression of the N-methyl-D-aspartate receptor subunit NR2B in the central amygdala, as well as increased mRNA of BDNF but decreased mRNA of serotonin receptor 1A in the dentate granule layer of the hippocampus (Neufeld et al., 2011). There are also many morphological differences between specific pathogen-free (SPF) and GF mice. For example, GF mice had delayed brain maturation and organization, evidenced by lower volumes and fractional anisotropy in major gray and white matter areas, as well as lower levels of myelination in total brain and major white and grey matter structures at either 4 or 12-weeks of age, which demonstrate delayed brain maturation and organization (Lu et al., 2018). This coincided with lower mobility and higher anxiety of GF mice in an open field test, which is a photo beam tracking method to monitor the movement of animals with two sets of infrared beams, at 4-weeks of age (Lu et al., 2018). At 12-weeks of age, GF mice also had reduced spatial and learning memory in the Morris water maize test, which measures spatial learning for subjects that use distal cues to navigate from start locations around the perimeter of an open swimming field to locate a submerged escape platforms. At this age, GF mice also exhibited reduced contextual memory in contextual fear conditioning test, which measures persistent freezing behavior using a foot shock context arena and a conditioned stimulus, in order to quantify hippocampus-dependent learning and memory test (Lu et al., 2018). Last but not least, in a three-chamber social test, which assesses cognition in the form of interest in a never-before-met intruder (i.e. social novelty), GF mice had reduced social novelty at 12-week of age. Similar behavioral changes were also observed in antibiotic-treated SPF mice (Desbonnet et al., 2015).

While the absence of gut microbiota leads to marked behavior changes, microbial colonization of GF mice reprogrammed the postnatal development of the HPA system. For example, the heightened HPA stress response in GF mice was attenuated by inoculation with *Bifidobacterium infantis*, but was enhanced by the enteropathogen *Escherichia coli* (Sudo et al., 2004). There appears to be a critical time window for microbiome inoculation to affect behavior in GF mice as fecal transplants from SPF mouse donor to 6 week old but not 8 week old GF mice reduced elevated HPA response in GF mice (Sudo et al., 2004). Early-life inoculation using SPF feces reduced the expression of postsynaptic density protein 95

(PSD-95) and synaptophysin in the striatum, which are involved in the neuronal circuits for motor control and anxiety behavior (Diaz Heijtz et al., 2011). Together these studies demonstrate that the presence of the commensal gut microbiota has dual functions in modulating both cognitive functions under basal conditions as well as stress response.

IV. Microbiome and neurotoxicants

IV-1. Air pollution.

Recent epidemiological studies have established a positive correlation between exposure to ubiquitous traffic-related air pollution and the exacerbations of various neurological disorders such as Alzheimer's disease and Parkinson's disease (Babadjouni et al., 2017; Calderon-Garciduenas et al., 2016). Large populations living in highly polluted metropolitan regions are at higher risk for robust central nervous system pathology (Babadjouni et al., 2017). The primary cause of urban air pollution is through vehicular emissions. Exposure to fine particulate matter (PM2.5) and ozone above US EPA standards, have been linked to both Alzheimer's and Parkinson's diseases (Calderon-Garciduenas et al., 2016; Palacios, 2017; Shin et al., 2018). Air pollution positively associates with the hallmark clinical characteristics of neuroinflammation and CNS diseases, including increased expression of pro-inflammatory markers in brain, diffused amyloid plaques, neuronal cell loss, and impaired cognition (Block and Calderon-Garciduenas, 2009). It has been suggested that inhaled particulate matter can directly translocate to the brain and cause neuroinflammation, which in turn contributes to neuro-degeneration (Calderon-Garciduenas et al., 2016; Oberdorster et al., 2005). In addition, the novel contribution of the gut-brain axis in several CNS disorders suggests that gut-derived pro-inflammatory signaling accompanied with dys-regulated microbial or host-derived lipid profiles may contribute to neurotoxicity (Russo et al., 2018; Valles and Francino, 2018). In human subjects, exposure to freeway air pollution correlated with decreased Bacteroidaceae and increased Coriobacteriaceae as well as increased fasting glucose levels (Alderete et al., 2018). In mice, inhalation of PM air pollution altered the composition of the gut microbiome and was suggested to play a role in PM-induced GI inflammation (Beamish et al., 2011; Kish et al., 2013; Mutlu et al., 2018). Because intestinal bacteria contribute to both local and systemic inflammation, the latter may lead to neuroinflammation (Grigg and Sonnenberg, 2017; Reinoso Webb et al., 2016). Investigation of the interplay among air pollution, gut microbiome, and inflammatory signaling is an intriguing direction in research on mechanisms of neurotoxicity.

IV-2. Antibiotics and drugs.

The important role of gut microbiome in the biotransformation of various therapeutic drugs has been extensively reviewed (Bisanz et al., 2018; Carmody and Turnbaugh, 2014; Haiser and Turnbaugh, 2013; Spanogiannopoulos et al., 2016). Briefly, gut microbiome can either utilize their own enzymes to metabolize drugs into reactive or inactive metabolites or can secrete endogenous microbial metabolites into circulation to interact with host receptors in various organs. We will focus on studies on gut microbiome and the drug categories that have neurotoxic side effects as summarized in Table 2. These drugs are selected based on Chapter 16 of the Casarett & Doull's Toxicology Textbook (Klaassen, 2013) as well as

literature search regarding the involvement of the gut microbiome in the metabolism and/or toxicities of these chemicals.

Microbiome and compounds associated with neuropathies.—The anti-cancer drug doxorubicin is known to produce progressive ataxia in laboratory animal models through degeneration of dorsal root ganglion cells and axonal degeneration (Graham and Lantos, 1997; Spencer and Schaumburg, 2000). In the human gut microbiome, doxorubicin can be inactivated by *Raoultella planticola* via reductive deglycosylation (Yan et al., 2018), thus targeting this bacteria is promising to reduce its side effects including neurotoxicity. Intestinal bacteria contribute to doxorubicin-induced intestinal damage (Rigby et al., 2016), whereas the dietary fiber pectin, which is a substrate of microbial fermentation, can reduce doxorubicin-induced intestinal inflammation through direct interaction with host Toll-like receptors 1 and 2 (Sahasrabudhe et al., 2018). In addition, gut microbiota can affect the efficacy of doxorubicin and many other anticancer drugs (Florez et al., 2016; Lehouritis et al., 2015), whereas doxorubicin can alter the gut microbial activity (Song et al., 2015). It may be interesting to investigate whether the interactions between doxorubicin and gut microbiota may modify the CNS toxicity.

MPTP (1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine) is an industrial chemical and contaminant of illicit narcotics that selectively destroys dopaminergic neurons of the nigrostriatal pathway, leading to Parkinsonian syndromes (Calne et al., 1985; Kopin, 1987). In mice, sub-chronic MPTP exposure affected the gut microbiome diversity, which was associated with sensorimotor performance and fear learning (Torres et al., 2018). Importantly, dysbiosis and GI dysfunction precedes motor dysfunction (Lai et al., 2018), whereas fecal microbiota transplantation from MPTP-exposed mice alone can induce motor impairment and striatal neurotransmitter decreased in normal mice (Sun, M.F. et al., 2018). Therefore, microbiota may mechanistically contribute to the pathogenesis of Parkinson's disease.

Microbiome and compounds associated with axonopathies.—The antibiotic and antiprotozoal drug metronidazole is a drug that can produce peripheral neuropathy (Goolsby et al., 2018), leading to axonal degeneration, lesions of cerebellar nuclei, mostly affecting myelinated fibers (Graham and Lantos, 1997; Spencer and Schaumburg, 2000). Studies showed that metronidazole also altered gut microbiota in the colon of healthy rats, evidenced by increased *Bifidobacteria spp*. (especially *Bifidobacterium pseudolongum*) and *Enterobacteria*, and this associated with increased mucus layer thickness (Pelissier et al., 2010). While this effect has been suggested to benefit the treatment of inflammatory bowel diseases, potential systemic effects following changes in the microbiota, especially on the CNS, need further investigation.

The antibiotic nitrofurantoin produces peripheral neuropathy via axonal degeneration (Spencer and Schaumburg, 2000). In human subjects with urinary tract infections, nitrofurantoin treatment correlated with a reduced relative abundance of the genus *Clostridium* and an increased relative abundance of the genus *Facalibacterium* (Stewardson et al., 2015), whereas another clinical study showed that nitrofurantoin treatment resulted in a temporary increase in *Bifidobacterium* (Vervoort et al., 2015). Overall, it is generally

considered that this drug only has a mild effect on the gut microbiota community, although the potential changes in microbial functions locally and in distal organs need additional investigations.

The anticancer drug cisplatin produces peripheral neuropathy evidenced by axonal degeneration and microtubule accumulation in early stages (Graham and Lantos, 1997; Spencer and Schaumburg, 2000). In mice, cisplatin treatment disrupts the gut microbiome as well as the mucosal integrity, and this can be partially corrected by Ruminococcus gnavus, which is one of the bacteria that is depleted by cisplatin, or by fecal gavage (Perales-Puchalt et al., 2018).

Microbiome and compounds associated with myelinopathies.—Amiodarone is an anti-arrhythmic drug that is known to produce myelinopathy (Graham and Lantos, 1997; Spencer and Schaumburg, 2000) as well as peripheral neuropathy following long-term high-dose therapy (Fraser et al., 1985). In rats, oral administration of *Lactobacillus casei* DN-114 001 slowed the absorption of amiodarone without altering the pharmacokinetics of its main metabolite (Matuskova et al., 2017); however, oral administration of *Escherichia coli* Nissel 1917 (EcN) increased the oral bioavailability of the parent compound as well as the P450-mediated metabolism (Matuskova et al., 2014). These studies at the single-strain resolution have suggested that targeting distinct microbiota can alter the pharmacokinetics and potentially the toxicity of amiodarone.

Disulfiram, which treats chronic alcoholism by inhibiting aldehyde dehydrogenase, produces peripheral neuropathy and swelling in distal axons (Graham and Lantos, 1997). Interestingly, disulfiram was repurposed as an antibiotic for multi-drug resistant *Staphylococcus aureus* infections, and it can increase the vancomycin susceptibility of three clinical vancomycin-resistant *S. aureus* strains (Long, 2017). The disulfiram metabolite diethyldithiocarbamate also has antibacterial activity towards *Bacillus anthracis* (Frazier et al., 2019). In addition, disulfiram-based disulfide derivatives have been shown to exhibit antibacterial activity against gram-positive *Staphylococcus*, *Streptococcus*, *Enterococcus*, *Bacillus*, and *Listeria spp.* (Sheppard et al., 2018). It remains unknown whether the antibacterial effect of disulfiram can affect the CNS.

Psychotropic drugs.—Several psychotropic drugs, including fluoxetine and escitalopram, have antimicrobial effects *in vitro* (Cussotto et al., 2018). Alternatively, lithium, valproate, and aripiprazole increased the richness and diversity of gut microbiome in human gut. In addition, escitalopram, venlafaxine, fluoxetine and aripiprazole have also been shown to increase the permeability in the ileum. Because it is known that microbiota plays an important role in regulating the gut-brain interactions, it has been suggested that the intestinal effect of the psychotropics may contribute to the mechanism of action and side effects of these medications (Cussotto et al., 2018).

IV-4. Metals and metalloids

Arsenic.—Arsenic is a carcinogenic metalloid that is widely distributed in nature in its trivalent (arsenic trioxide and sodium arsenite) and pentoxide forms (sodium arsenate, arsenic pentoxide, and arsenic acid). Other organoarsenicals are also common. Occupational

exposure to arsenic compounds comes in the form of pesticides, herbicides, and other agricultural products. Environmental arsenic is in drinking water with sources in the United States less than 5 μg/L (Environmental Protection Agency maximum contaminant limit is 10 μg/L), however it is estimated that many people in Bangladesh drink water in excess of 50 μg/L (Klaassen, 2013). Acute exposure to arsenic has many symptoms, including fever, anorexia, hepatomegaly, melanosis, cardiac arrhythmia, and terminal cardiac failure, as well as a delay in sensory loss in the peripheral nervous system (Wallerian degeneration of axons) (Klaassen, 2013). Chronic arsenic exposure can cause diffuse or spotted hyperpigmentation or hypopigmentation, as well as liver injury. Interestingly, peripheral neuropathy also occurs with the development of numbness or “pins and needles” in the hands and feet, caused by dying-back axonopathy with demyelination.

From environmental observations, there was a non-significant trend in microbiome composition dependent on arsenic contamination observed in soil and earthworm microbiome samples around an arsenic mine, with about 47 taxa (about 7% of the abundance) driving the differences (Pass et al., 2015). Zebrafish exposed to varying low concentrations of arsenic (10, 50, and 100 ppb for 20 days) found 43 amplicon sequence variants that increased in abundance and 43 that decreased at the genus level (Dahan et al., 2018).

The Simulator of the Human Microbial Intestinal Ecosystem (SHIME) system is a dynamic series of six compartments and pumps that are used to mimic the intestines by controlling the pH, relative volume of fluid, and residence time, as well as the inoculation of the human microbiome (Joly et al., 2013; Requile et al., 2018). Regarding arsenic toxification and detoxification via methylation by gut microbiome, a study using the human SHIME model showed that arsenite (As[II]) is more readily metabolized than arsenate (As[V]), 66.5–92% to 22.1–38.2% respectively (Yin et al., 2015), and gut microbiota can also release arsenic from the soil in solid phase for absorption (Yin et al., 2017). Another SHIME model demonstrated that co-administration of drinking water with ferric iron and arsenic increased arsenic methylation and decreased absorption in the colon. Effluents from iron-exposed SHIME colons decreased toxicity in the human hepatoma cell line HepG2 cells (Yu et al., 2016). *Bacteroides spp.*, *Clostridium spp.*, *Alistipes spp.*, and *Bilophila spp.* had resistance to and ability to methylate arsenic (Yu et al., 2016).

Several mouse studies have looked at the effect of arsenic exposure on the microbiome using 16S rDNA gene sequencing data. One of the first arsenic microbiome studies exposed C57BL/6 mice to 10 ppm arsenic in drinking water for 4 weeks and showed clear microbiome compositional differences between control and exposed mice with 2 microbial classes increased and 7 classes decreased (Lu et al., 2014). Another study showed that microbiome compositional and functional changes could be sex-specific (Chi et al., 2016), and a follow-up study exposing mice to 100 ppb arsenic for 13 weeks showed altered abundance of microbial genes involved in carbohydrate metabolism, especially pyruvate fermentation, short-chain fatty acid synthesis, and starch utilization, as well as stress response genes (Chi et al., 2017a). However, mice exposed to arsenite (10 or 250 ppb) did not have altered expression of arsenate reductase (arsA) or the arsenite exporter (arsB), thus

bacteria with genes protective against arsenic may not be the bacteria that were increased during arsenic exposure (Dheer et al., 2015).

Importantly, Coryell et al. (2018) showed that GF mice and antibiotic-treated conventional mice exposed to arsenate (25 and 100 ppm) excreted less arsenic in stool and accumulated more arsenic in organics relative to control mice. GF arsenite methyltransferase (As3mt)-knockout mice are hypersensitive to arsenic-induced mortality but are protected following human fecal microbiome transplants, likely in part due to protective properties of *Faecalibacterium prausnitzii* (Coryell et al., 2018). Similarly, antibiotic-treated mice exposed to arsenite (III; 250 ppb and 1 ppm) had increased total urinary arsenic, but decreased fecal arsenic than conventionally raised mice, indicating that a depleted microbiome could absorb more arsenic (Chi et al., 2019). This evidence suggests that gut microbiota may limit the arsenic absorption, but no conclusions are definitive between arsenic-induced microbiome neurotoxicity. Additionally, many of the studies used exposures greater than the described human exposures (50 ppb or 50 μg/L in the population from Bangladesh); therefore, translational conclusions regarding arsenic exposure and microbiome in humans should remain cautious.

Copper.—Copper is a trace element found in all tissues and is required for a plethora of molecular events including cellular respiration, peptide amidation, neurotransmitter biosynthesis, pigment formation, and connective tissue strength. Copper is present throughout the brain with many enzymes in the CNS being copper-dependent for proper function. Both a deficiency and an excess of copper due to genetics or environmental factors can lead to several neurological conditions, including aceruloplasminemia, Alzheimer's disease, amyotrophic lateral sclerosis, Huntington's disease, Menkes disease, occipital horn syndrome, Parkinson's disease, prion disease, and Wilson disease (Desai and Kaler, 2008). Copper ions are naturally antimicrobial, but very few papers have investigated the antimicrobial properties of copper on the gut microbiome. Culturing of chicken ileal microbiome exposed to copper increased *Lactobacillus spp.* while decreasing *Escherichia coli*, but the effect of copper on the *in vivo* microbiome was negligible (Pang et al., 2009). Supplementation of copper to dairy calves for 75 days increased the richness of the rumen microbiome and decreased the lipopolysaccharide biosynthetic pathway (Biscarini et al., 2018). It appears that copper supplementation, not necessarily excess copper, may alter the microbiome composition, but it is unclear if this may play a role in copper neurotoxicity.

Gold.—Elemental gold is considered nontoxic and is used as an aesthetic enhancement in food and drinks. However, gold in its ionic form can have neurotoxic effects. For example, used as an anti-inflammatory treatment for rheumatoid arthritis, gold sodium thiomalate decreases the number of unmyelinated axons, suggesting gold could slow signal response to the peripheral nervous system (Levine et al., 1986; Salzer and Zalc, 2016). A study investigating gold nanoparticle protection against colitis also identified a gut dysbiosis in mice following 8 days of exposure with decreased species richness as well as decreased *Lactobacillus spp.* and other SCFA-producing bacteria (Kase et al., 1987). Further research is needed to understand the effect of ionic gold on the gut microbiome and neurotoxicity.

Lead.—Lead is a non-essential, heavy metal toxicant that can cause severe neurotoxicity with the EPA dictating the action level at 15 ppb. Adults can be exposed to lead through contamination of drinking water via lead pipes or by its natural occurrence in the environment, as well as in occupational settings such as smelting and soldering. Children can also be exposed through mouthing or consuming objects other than food, such as dust and lead contaminated paint. Children more readily absorb lead compared to adults with limited protection by the developing blood-brain barrier (Perlstein and Attala, 1966). Shown in Figure 2A, lead concentrations in mussels on the coastal regions of the US are highest on the East coast between Washington and Boston with large areas of exposure around the Lake Erie region in northern Ohio, Chicago, and along the West coast near San Francisco and Seattle (see Methods for GIS data analysis). Concentrations of lead in bivalves ranged from 0.172 to 73.6 μg/dry g. Large acute exposures result in severe cerebral edema, likely due to damaged endothelial cells, with children more likely to develop lead encephalopathy than adults (Johnston and Goldstein, 1998). Although not well understood, chronic lead exposure results in peripheral neuropathy and can also include gastritis, abdominal pain, anemia, and deposits of lead in gums and long bones.

Animal studies showed that lead exposure (acute, chronic, and perinatal) alters the composition of the gut microbiome, which may contribute to metabolic disorders. For instance, perinatal lead exposure in drinking water (32 ppm; 2 weeks before mating to postnatal day 21) increased the adult body weight of male mouse offspring, but not female offspring, and this was highly associated with microbiome compositional change, suggesting that lead-exposed gut microbiome may play a role in sex-specific differences (Wu et al., 2016). Adult female C57BL/6J mice exposed to lead (10 ppm) for 13 weeks decreased the abundance of the genera *Blautia*, *Coprococcus*, two species of *Ruminococcus*, and 1 genus in each of the families *Clostridiales* and *Lachnospiraceae*, as well as increased abundance of a genus in the *Clostridiaceae* family (Gao et al., 2017c). Lead exposure also reduced microbial metabolites in the vitamin E and bile acid pathways as well as altering the gene abundance for nitrogen metabolism and energy metabolism (Gao et al., 2017c). Dysregulated energy metabolism and altered microbiome composition were also found in 5-week-old mice exposed up to 0.1 mg/L (0.1 ppm) of lead for 15 weeks; a dose-dependent decrease in the phylum Bacteroides and an increase in Firmicutes was observed (Xia, J. et al., 2018a). Adult male zebrafish exposed to 0.03 mg/L (0.03 ppm) lead for 7 days had an increase in Firmicutes, but a decrease in Proteobacteria; in total 30 genera were altered by acute lead exposure (Lai et al., 2018). Many of the microbiome-lead exposure studies identified changes in gut microbiome, however the exposures are greater than the EPA action limit of 15 ppb and no studies related the changes in microbiome to neurotoxic effects in the host. More studies are needed to identify if gut microbiome is a contributing factor to lead-induced neurotoxicity.

Magnesium.—Magnesium is an important cofactor that helps regulate diverse chemical reactions in the body, including cardiovascular, alimentary, endocrine, and osteoarticular systems, as well as brain biochemistry by influencing neurotransmission pathways associated with depression (Rajizadeh et al., 2017; Serefko et al., 2016). Mice exposed to a magnesium-deficient diet for 6 weeks had increased depressive-like behaviors and a gut

microbiome composition correlated with magnesium deficiency (Winther et al., 2015). However, it is unclear if the compositional changes in gut microbiome contribute to the observed depressive-like behaviors.

Manganese.—Manganese is an essential trace element needed for many enzymatic reactions, such as arginase and glutamine synthatase. Excessive consumption of manganese can lead to Parkinson's disease-like symptoms, including dysfunction of the basal ganglia (Dobson et al., 2004). In the United States, the highest concentration of manganese in bivalves is in northern Ohio and northwestern New York around the Great Lakes region (Lake Erie and Lake Ontario; Figure 2A). Adult mice exposed to neurotoxic concentrations of manganese for 13 weeks induced a gut dysbiosis for 12 genera in female mice and 16 genera in male mice. Furthermore, there was an increase in microbial tryptophan synthesis pathways in females, but in males, there was a general decrease in GABA/Putrescine metabolism (Chi et al., 2017b). Again, it is not known if the changes in gut microbiome contribute to manganese toxicity.

Mercury and methylmercury.—Elemental mercury (Hg) is a heavy, silvery liquid metal that is used in products such as thermometers, barometers, float valves, and fluorescent lamps. Exposure to elemental mercury may cause emotional disturbances, tremors, and fatigue, but there is limited evidence of toxicity in humans (Klaassen, 2013). The National Institute for Occupational Safety and Health (NIOSH) limits occupational exposures to 0.05 mg/m^3 (about 6 ppb) over a 10-hour workday and the EPA limits mercury to 2 ppb in drinking water. In the context of the microbiome, one study examined the development of Hg and antibiotic resistance in bacteria of the estuarine fish mummichog (*Fundulus heteroclitus*) upon exposure to Hg in the diet for 15 days. The microbiome of fish exposed to mercury developed resistance to at least 3 antibiotics compared to control fish; furthermore, there was an 8-fold increase in the mercury resistance gene mercuric reductase at a mercury contamination site (Lloyd et al., 2016). This indicates that mercury exposure induced the co-selection of mercury and antibiotic resistance. An epidemiological study of pregnant women and children found that consumption of probiotic yogurt was protective against increased blood levels of mercury and arsenic in pregnant women but not children (Bisanz et al., 2014). Interestingly, a combinational exposure of copper and mercury in female Kunming mice decreased the abundance of the genera *Sporosarcina, Jeotgailcoccus*, and *Staphylococcus*, but increased the genus *Anaeroplasma* (Ruan et al., 2018). It is unclear how the shift would affect neurotoxicity, but this demonstrates the need to consider mixtures when assessing risk.

Methylmercury (organic mercury) is highly toxic, causing neuronal degeneration, ataxia, paresthesia, and psychomotor retardation in adults (Klaassen, 2013). In children, exposure to methylmercury can cause developmental disabilities, retardation, and cognitive deficits, which is attributed to an immature blood-brain barrier and higher disposition of mercury in the developing brain. In an epidemiological study, methylmercury concentration in the stool or total mercury in hair of pregnant women (36–39 weeks gestation) was correlated with 17 bacterial genera, but there was no detection of the mercury methylation gene or the methylmercury detoxification genes (Rothenberg et al., 2016). The inability to identify

known mercury biotransformation genes in the gut microbiome of pregnant women could be attributed to small sample size (n=6) or there could be exciting new alternative pathways for microbial mercury metabolism. One group cultured the microbiome of two human subjects to investigate methylmercury metabolism rate in relation to nutrients; there was a dependency of diet on demethylation of methylmercury by an increase in protein content, but the responsible genes and mechanism could not be identified (Guo, G. et al., 2018). Changes in gut microbiome following dietary exposure to methylmercury is further supported by a study in fathead minnows which showed significant compositional differences between methylmercury exposed and unexposed groups with 18 genera altered by exposure (Bridges et al., 2018). They found an increase in bacteria that generally have genes for xenobiotic metabolism and metal removal, including Deltaproteobacteria FAC87, *Xanthomonadaceae*, *Comamonadaceae, Cloacibacterium spp.*, and *Pirellula spp.* (Bridges et al., 2018). Overall, more studies at human relative exposures are needed to conclude the effect of mercury and microbiome on host neurotoxicity.

IV-5. Persistent environmental toxicants.

PCBs.—Polychlorinated biphenyls (PCBs) were formerly used in industrial and consumer projects before they were banned in the United States in 1979. Due to their bio-accumulative nature, these persistent environmental contaminants are still of significant public health concern and are listed on the 2015 Agency for Toxic Substances and Disease Registry Substance Priority List (http://www.atsdr.cdc.gov/SPL/index.html). PCBs are frequently detected in fatty food (Gorchev and Jelinek, 1985; Newsome et al., 1998), air in public schools (Herrick, 2010; Herrick et al., 2016), industrial paint pigments (Anezaki and Nakano, 2014; Hu and Hornbuckle, 2010), as well as human samples including blood, adipose, milk, and placenta (Nakagawa et al., 1987; Suzuki et al., 2005; Wang et al., 2010). In humans, epidemiological studies showed a positive link between developmental PCB exposure and neurological deficits in infants and children (Korrick and Sagiv, 2008; Schantz, 1996; Winneke, 2011). Symptoms associated with PCB neurotoxicity include decreased motor and cognitive skills in newborns, greater incidence of behavioral problems and lower IQ scores in children, and lower cognitive functioning in older adults (Przybyla et al., 2017; Ribas-Fito et al., 2001; Schantz, 1996). Developmental neurotoxicity following PCB exposure has also been observed in laboratory animals including mouse and rat pups, as well as chicken embryos (Kania-Korwel et al., 2017; Roelens et al., 2005; Yang et al., 2009) and in neuronal cell cultures (Lyng and Seegal, 2008; Lyng et al., 2007). Suggested molecular mechanisms of PCB neurotoxicity include binding to aryl hydrocarbon receptor (for dioxin-like PCB congeners), decreasing dopamine content, GABAergic neuronal dysfunction, interference with calcium signaling, as well as altering the dendritic growth and plasticity by promoting the activity of ryanodine receptors (Lyng et al., 2007; Tilson and Kodavanti, 1998; Yang et al., 2009).

As shown in Figure 2B, Concentrations of PCB-95 in bivalves ranged from 0.12 to 153.88 ng/dry g while concentrations of PCB-153 ranged from 0.04 to 472.5 ng/dry g. Similar to PBDEs, concentrations of both PCB congeners tended to increase with increasing proximity to coastal cities with large populations, with overall higher concentrations of PCB-153

measured. One exception to this trend appears south of Miami, Florida where PCB-95 is present in higher concentrations than PCB-153.

Coinciding with PCB-associated neurodevelopmental disorders, there is strong evidence that intestinal dysbiosis also plays a role in the etiology of these diseases (Borre et al., 2014; Warner, 2019). In adult mice, oral exposure to an environmentally relevant PCB mixture (PCB-153, PCB-138, and PCB-180) was shown to decrease the levels of *Proteobacteria* correlating with the activity level of the mice, whereas exercise attenuated PCB-induced changes in gut microbiome (Choi et al., 2013). Dioxin-like PCB-126 increased both intestinal and systemic inflammation correlating with gut dysbiosis (Petriello et al., 2018). Gut dysbiosis may lead to altered microbial metabolites as well as increased pro-inflammatory cytokines in circulation. Oral exposure to PCBs increased pro-inflammatory mediators in brain and other metabolic organs (Chi et al., 2018; Sipka et al., 2008). Because systemic inflammation has been linked to neuroinflammation (Bendorius et al., 2018), it is possible that PCB-induced gut dysbiosis contributes to PCB-induced neurotoxicity partially through inflammation. In addition, there is a positive association between circulating glucagon-like peptide-1 (GLP-1) and *Bifidobacterium spp*. following PCB-126 exposure (Petriello et al., 2018) with GLP-1 protecting against neurotoxicity of various etiologies (Athauda and Foltynie, 2016; Chang et al., 2018; Khalilnezhad and Taskiran, 2018).

PBDEs.—Polybrominated diphenyl ethers (PBDEs) are a class of persistent environmental contaminants that were previously used as flame retardants in various consumer products. Although the commercial use of PBDEs has been recently banned in the United States, PBDEs are still ubiquitously found in the environment due to their resistance to degradation, bio-accumulation along the food chain, as well as the recycling of PBDE-containing products worldwide (Schecter et al., 2010; Schecter et al., 2003). PBDE levels in human specimens, such as blood, breast milk, and adipose tissue, have increased exponentially over the last 30 years, and are especially high in North America as compared to European and Asian countries (Costa et al., 2014; Costa and Giordano, 2007). Infants and toddlers are particularly vulnerable to PBDE-induced adverse effects due to exposure to PBDE-contaminated breast milk and dust (Costa et al., 2014). In contrast to many studies, a 2017 study in middle-aged and older Californian women showed a modest average annual percent increase in serum concentrations of 3 major PBDE congeners (BDE-47, BDE-100, and BDE-153) from 2011 to 2015 (Hurley et al., 2017). The Geographic Information System (GIS)-based distribution of 2 breast milk-enriched PBDE congeners (BDE-47 and BDE-99) in coastal areas of the United States is shown in Figure 2C. Concentrations of BDE-47 in bivalves ranged from 0.3 to 68.4 ng/dry g and concentrations of BDE-99 ranged from 0.2 to 38.4 ng/dry g. The concentrations of both congeners tended to increase with proximity to a major coastal city, and overall higher concentrations of BDE-47 measured. Higher brominated congeners are thought to debrominate into lower forms through photolytic degradation, which possibly explains this overall trend (Lagalante et al., 2011). BDE-47 was present in notably higher concentrations than BDE-99 near Houston, Texas, Biloxi, Mississippi, Mobile, Alabama, and Tampa, Florida.

PBDEs are present in 97% of adults in the United States as measured by the National Health and Nutrition Examination Survey (NHANES), with BDE-47 and BDE-99 present in the

highest serum concentrations (Sjodin et al., 2008). Pregnant Mexican immigrant women living in California were found to have increasing levels of total PBDEs with each year of residence as measured by the Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) cohort, with BDE-47 the most common congener found (Castorina et al., 2011). In fact, BDE-47 can reach higher levels in Americans than total PBDE levels in humans in other countries (Fromme et al., 2009). For 223 Mexican women living in California as measured through the CHAMACOS cohort, increasing total PBDE (including BDE-47 and BDE-99) serum concentrations were associated with lower chance of pregnancy (Harley et al., 2010).

PBDEs have been linked to developmental neurotoxicity. A 2018 review and meta-analysis of animal evidence showed that exposure to BDE-47, BDE-99, and BDE-209 affects learning (Dorman et al., 2018). In humans, large prospective cohorts showed that *in utero* exposure to PBDEs is associated with impaired executive function and poor control of attention in children and that prenatal and postnatal PBDE exposure adversely impact externalizing behavior (Vuong et al., 2018). However, the exact mechanisms of PBDE-induced neurotoxicity in humans is unknown. In mice and rats, perinatal PBDE exposure at environmentally relevant concentrations produced persistent changes in spontaneous motor activity, including hyperactivity and decreased habituation, as well as disruptions in learning and memory (Costa and Giordano, 2007). Proposed mechanisms of PBDE developmental neurotoxicity include reduction of circulating thyroid hormones, induction of apoptotic cell death of neurons and astrocytes, oxidative stress-induced damage, interference with calcium signaling and neurotransmitters, as well as biotransformation of PBDEs (Costa et al., 2014; Costa and Giordano, 2007; Giordano et al., 2008). In zebrafish, developmental neurotoxicity of DE-71 (a commercial PBDE mixture) decreased expression of genes involved in central nervous system development and decreased locomotion activity (Chen et al., 2012).

Investigation of the involvement of gut microbiome in PBDE-induced neurotoxicity is still at an early stage. We hypothesize that PBDE neurotoxicity may be regulated through the gut-liver axis. This hypothesis is based on 1) the evidence that PBDEs are primarily oxidized by hepatic cytochrome P450s (CYPs) into hydroxylated metabolites, which are considered more toxic than the parent compound (Dingemans et al., 2008), and 2) the observations that the hepatic P450 levels are profoundly modified by lack of gut microbiome in mice (Kuno et al., 2016; Selwyn et al., 2015; Toda et al., 2009). In primary adult neural stem/progenitor cells isolated from subventricular zone of mice, the hydroxylated BDE-47 metabolite 6-OH-BDE-47, but not its parent compound, inhibited adult neurogenesis demonstrated by decreased survival, proliferation, and neuronal differentiation associated with inhibition of ERK5 signaling (Li et al., 2013). We have reported that in BDE-47 orally exposed GF mice, there was an increase in 5-OH-BDE-47 but lower levels of 4 other BDE-47 hydroxylated metabolites in liver; whereas in BDE-99 orally exposed GF mice, there was a decrease in 4 minor BDE-99 hydroxylated metabolites in liver (Liu, Q. et al., 2017). Interestingly, the lack of gut microbiome potentiated PBDE-mediated up-regulation of Cyp1a2 and Cyp3a11 at both mRNA and protein levels in mouse liver (Liu, Q. et al., 2017). We also showed that in large intestinal content of adult male mice, PBDEs induced a dysbiosis, including an increase in *Akkermansia muciniphila* and *Erysipelotrichaceae Allobaculum spp.*, positively associated with increased unconjugated bile acids in serum as well as increased DNA

abundance in microbial 7α-dehydroxylation enzymes involved in secondary bile acid synthesis (Li et al., 2018). Although evidence in humans is limited, it has been shown in mice that deoxycholic acid (a microbial-derived secondary bile acid) may contribute to a neurological decline (McMillin and DeMorrow, 2016; McMillin et al., 2016). Microbial metabolic functions in the intestine have also been shown to be altered by DE-71 in zebrafish, associated with disruption of neural signaling, epithelial barrier integrity, inflammatory response, oxidative stress, and compromised detoxification potential in males (Vuong et al., 2018). Similar to the studies on heavy metal exposure, a mechanism linking microbiome and PBDE-induced neurotoxicity remains elusive.

Organochlorines.—Organochlorines are a class of pesticides that include dichlorodiphenyltrichloroethane (DDT) and hexachlorocyclohexane (HCH), which were banned in the 1970s and 1980s due to their reproductive (Salihovic et al., 2016), neurobehavioral (Saeedi Saravi and Dehpour, 2016), and immunological (Mrema et al., 2013) toxicities, as well as carcinogenicity (Freund et al., 2014). In addition, organochlorines are environmentally persistent (Jayaraj et al., 2016), and are still detected in Atlantic bluefin tuna (*Thunnus thynnus*), an indicator organism for the oceanic environment and therefore a potential risk to human health if consumed chronically (Maisano et al., 2016). Chronic exposure to the major metabolites of DDT, dichlorodiphenyldichloroethylene (p,p'-DDE) and β-hexachlorocyclohexane (β-HCH), in mice altered the composition of the gut microbiota and increased the presence of bacteria with microbial bile salt hydrolase, which is required for the production of secondary bile acids (Liu, Q. et al., 2017). However, it is unclear how the metabolites modified the gut microbiota and how this may contribute to organochlorine neurotoxicity.

IV-6. Pesticides

Carbamates.—Carbamates are derived from carbamic acid that kill insects by reversible inhibition of acetylcholinesterase (AChE). The inhibition of AChE prevents the degradation of the neurotransmitter acetylcholine causing over-stimulation of a nerve or muscle, resulting in exhaustion and tetany (Fukuto, 1990). Carbamate pesticide has increased along with organophosphorus compounds and some compounds can have toxicities for mammals and aquatic organisms.

In the rumen microbiome of cows, Ufarté et al. (2017) identified a bacterium named clone 44I12 that could metabolize the carbamate fenobucarb to a less toxic compound, but not two other carbamates tested, fenoxycarb and prosulfocarb (Ufarte et al., 2017). The carbamate-specific metabolism by microbes is similar to a study that isolated bacteria which could metabolize fenobucarb from rice paddy soils, but not other carbamates (Kim et al., 2014). However, neither of these studies associated the microbiome to neurological health. Consumption of aldicarb in drinking water of C57BL/6 mice for 13 weeks resulted in a differential abundance of 17 genera and also significantly disrupted the brain metabolism marked by a reduction in glucose and malic acid, whereas 3-hydroxybutyric acid was increased (Gao et al., 2018b). Although toxicity was not shown to be dependent on a gut dysbiosis, this study demonstrated a potential association between aldicarb, neurotoxicity, and gut microbiome.

Neonicotinoids.—Neonicotinoids are a popular and growing class of insecticide thought to selectively and irreversibly target the nicotinic acetylcholine receptors in the CNS of insects, making them generally safe for humans and animals (Han et al., 2018). Because of this selectivity, neonicotinoids also increase the mortality of pollinators, such as honey bees (*Apis mellifera*) (Ihara and Matsuda, 2018). For example, imidacloprid, the first neonicotinoid, suppresses immune function and increases the risk of pathogen-infection in honey bees (Di Prisco et al., 2013). Using *Drosophila melanogaster* (fruit fly) as a model for honey bees, it was shown that sublethal exposure to imidacloprid induced a gut dysbiosis and decreased survival following *Serratia marcescens* infection (Daisley et al., 2017). However, a study examining this effect in honey bees showed that decreased survival due to imidacloprid exposure and metabolism of the compound is not gut microbiome-dependent (Raymann et al., 2018).

Organophosphates.—Organophosphates (OPs) are esters of phosphoric acid that covalently bind to AChE, causing over-stimulation of neurons (Ruark et al., 2013). More recently, some OPs are recognized to have off-target toxicities at concentrations below the inhibition of AChE. For example, some OPs can inhibit or activate serine hydrolases and inhibit cannabinoid receptor 1 (CNR1) (Casida and Quistad, 2004). Diazinon exposure can also alter signaling of the neurotransmitter serotonin, production of which is influenced by the microbial metabolites short-chain fatty acids (SCFAs) and tryptophan (Slotkin et al., 2008; Timofeeva et al., 2008; Waclawikova and El Aidy, 2018). Gao et al. (2017b) demonstrated that C57BL/6 mice exposed to diazinon in drinking water for 13 weeks altered gut microbiome composition (19 genera), function, and metabolic profiles in a sex-specific manner (16S rDNA sequencing and whole genome shotgun sequencing) (Gao et al., 2017b), including decreased tryptophan synthase, which is required for the biosynthesis of tryptophan in bacteria. In a follow-up study, metatranscriptomic analysis revealed an increase in the RNA of quorum sensing genes as well as bacterial motility and sporulation, which could explain the detection of pathogenic bacteria (Gao et al., 2017a). Similarly, C57BL/6 male mice exposed to malathion for 13 weeks exhibited increased DNA expression of quorum sensing, motility, and pathogenicity genes, indicating that exposure to some OPs may increase the gut microbiota susceptibility to colonization by pathogenic bacteria (Gao et al., 2018a). One study compared the gut microbiome of the malaria vector-containing mosquito *Anopheles albimanus* and demonstrated that mosquitos resistant to the OP fenitrothion had a relatively lower diversity than mosquitos who were not resistant, possibly due to fenitrothion-exposure selecting for a few bacteria which utilize fenitrothion as an energy source, leading to their overabundance (Dada et al., 2018). Interestingly, BALB/c mice exposed to monocrotophos for 180 days had increased production of the microbial SCFA acetate and show that increased acetate induced gluconeogenesis and glucose intolerance (Velmurugan et al., 2017). Fecal microbiome transplants of monocrotophos-exposed mice to un-exposed mice showed that glucose intolerance was microbiome-dependent. In humans, an examination of the oral microbiome of farmworkers by season demonstrated that microbiome perturbations may act persistently as the dysbiosis persisted in winter after the potential for exposure during the spring and summer (Stanaway et al., 2017). Therefore, while the majority of these chemicals have not been investigated for gut microbiome-dependent neurotoxicity, it has been noted that gut dysbiosis causes

neurotoxicity via multiple mechanisms (Galland, 2014), thus exposure to chemicals such as carbamates could potentially further these effects.

Chlorpyrifos is the most well studied OP insecticide in relation to changes in the microbiomes of humans and animal models, with some evidence for neurotoxic effects. Most notably, adult male Wistar rats exposed to chlorpyrifos for 9 weeks increased bacteria associated with neurotoxicity such as *Candidatus Arthromitus*, in addition to inducing metabolic disorders (obesity and diabetes) (Fang et al., 2018). Rats exposed perinatally to chlorpyrifos had altered gut microbiome profiles as adults and were associated with impaired epithelium protection (Joly Condette et al., 2015) and induced metabolic disorders, but these conditions were partially abrogated by inulin supplementation (Reygner et al., 2016b). The microbial metabolites SCFAs and bile acids were altered in the urine of mice exposed to chlorpyrifos for 30 days (Zhao et al., 2016). The metabolome profiles correlated with changes in gut microbiome. Increased lipopolysaccharide, intestinal inflammation, and intestinal permeability indicates that the perturbations of the mouse microbiome by chlorpyrifos significantly affect gut health and the microbial metabolites that can act as signaling to the host (Zhao et al., 2016). Zebrafish exposed to chlorpyrifos also had altered gut microbiome composition (25 taxa) as well as metabolic changes in glucose and lipid metabolism, TCA cycle, and amino acid metabolism (Wang, X. et al., 2019). In the SHIME model, chlorpyrifos decreased the colony forming units (cfu) of *Bifidobacterium spp*. and *Lactobacillus spp*. after 15 to 30 days of exposure (Requile et al., 2018). Decreased *Bifidobacterium spp*. and *Lactobacillus spp*. was reflected in two other SHIME studies, as well as increased *Entereoccocus spp*. (Joly et al., 2013; Reygner et al., 2016a).

Two other environmentally relevant animal models, which have been used to explore gut microbiome-chlorpyrifos interactions, are the diamondback moth (*Plutella xylosterlla*) and fruit fly (*Drosophila melanogaster*). The diamondback moth is an economically deleterious pest of cruciferous crops, and it is suspected that the development of pesticide-resistance is partly due to the microbiome of this insect. *In vitro* experiments from bacteria isolated from the gut microbiome of the diamondback moth revealed that *Enterococcus spp*., vitamin C, and acetylsalicylic acid enhanced resistance to chlorpyrifos; however, the bacteria do not detoxify the insecticide (Xia, X. et al., 2018). An earlier sequencing study found that an insecticide resistant line of diamondback moth larva had increased *Lactobacillales*, *Pseudomonadales*, and *Xanthomondales* (Xia et al., 2013). Contradictorily, GF and antibiotic treated fruit flies exposed to chlorpyrifos lived significantly longer than conventionally raised flies, and this was due to metabolism of chlorpyrifos to the stronger AChE inhibitor chlorpyrifos oxon by *Lactobacillus plantarum* (Daisley et al., 2018). This effect was mitigated by supplementation of the human probiotic *Lactobacillus rhamnosus* GG, which binds, but does not metabolize chlorpyrifos as demonstrated in a previous study along with *L. rhamnosus* GR-1 (Trinder et al., 2016). Studies in the diamondback moth and fruit fly demonstrate that certain bacteria species can increase or decrease the toxicity of chlorpyrifos.

Overall, microbiome may contribute to neurotoxicity and other toxicological endpoints due to organophosphate exposure, but more evidence (behavior and biochemical data) is needed to ascertain a direct mechanism of OP exposure to gut dysbiosis to neurotoxicity.

Pyrethrins.—Pyrethroids are derived from the chrysanthemum flower (originally known as pyrethrum) and are found in many household insecticides and repellents. Pyrethroids prevent the closure of voltage-gated sodium channels, making them axonic excitotoxins that prevent repolarization that leads to paralysis of an affected organism. Pyrethroids are broad spectrum pesticides, affecting insects indiscriminately, including bees, but are poorly absorbed by humans and often are used to treat clothing and prevent mosquito-borne diseases.

Permethrin has been linked to the depressive- and anxiety-like behavior of Gulf War Illness (GWI), as well as reduced hippocampal volume, neural stem cell activity, and neurogenesis (Parihar et al., 2013). Co-exposure of permethrin and another GWI compound pyridostigmine bromide in a mouse model decreased *Lactobacillus spp*. and *Bifidobacterium spp*. and supplementation of the microbial SCFA butyrate restored gut homeostasis (Seth et al., 2018). Chronic exposure to permethrin in rats decreased abundance of the beneficial bacteria *Bifidobacterium spp*. and *Lactobacillus paracasei* in the feces (Nasuti et al., 2016). Overall, pyrethrins, and specifically permethrin, have an effect on the microbiome, but more research is needed to identify if changes in the gut microbiome are associated with the neuroinflammation and behavioral changes associated with GWI.

Rotenoids.—Rotenoids are naturally occurring substances, particularly in the flowering plant subfamily *Faboideae* as well as *Nyctaginaceae*. Many rotenoids such as rotenone have broad spectrum insecticidal properties. A hydrophobic compound, rotenone is an inhibitor of the mitochondrial complex I that easily crosses the blood-brain barrier causing toxicity to the central nervous system. Specifically, rotenone selectively induces apoptosis in serotonergic and dopaminergic neurons (Bisbal and Sanchez, 2019; Ren and Feng, 2007; Ren et al., 2005). Interestingly, rotenone exposure in Lewis rats for 7 days induces the pathology of Parkinson's disease and is therefore used in animal models for Parkinson's disease (Betarbet et al., 2000; Bisbal and Sanchez, 2019). In mice orally exposed to rotenone for 28 days, were shown to have 14 bacteria taxa at the family level dysregulated with a marked decrease in *Bifidobacterium spp*. (30099890). Furthermore, dopaminergic cell loss was inversely correlated with increased *Rikenellaceae*, *Erysipelotrichaceae*, *Ruminococcaceae* and *S24–7*, as well as a positive correlation with *Bifidobacteriaceae*. A second study in mice that used unpredictable restraint stress for 12 weeks and 6 weeks of rotenone exposure found that rotenone exposure furthered the restraint stress-associated increase in the relative abundance of the mucin-degrading bacteria *Akkermansia muciniphila* (Dodiya et al., 2018). This result is interesting because an increase in *A. muciniphila* has been noted in patients with Parkinson's disease, possibly due to the bacterium's ability to activate TLR2 as explored in a review by Radisavljevic et al (Radisavljevic et al., 2018). In a 4-week longitudinal rotenone exposure study in mice, gastrointestinal dysfunction started at 3 weeks along with significant inflammation; rotenone also decreased the microbial richness at 3 weeks compared to baseline with decreased in Bacteroidetes and increased Firmicutes (Yang et al., 2017). However, in adult male rats exposed to rotenone for 4 weeks, there was a tendency for *Lactobacillus spp*. and *Bifidobacterium spp*. to increase despite matching intestinal inflammatory properties (Johnson et al., 2018). It should be noted that some species of *Lactobacillus* produce D-lactic acid, which can cause neurological effects (Yilmaz et al., 2018). Overall, it is unclear if gut microbiome altered by rotenone may contribute to

Parkinson's disease or if rotenone neuronal toxicity induces a gut dysbiosis; further studies are necessary to identify mechanisms of toxicity and disease pathology.

Herbicides and fungicides.—In general, herbicides and fungicides are designed to prevent and kill unwanted plants, molds, and fungi; however, their chemical properties can have unintended neurotoxicity and hormonal disruption in humans and animals. For example, atrazine, a triazine herbicide used in corn and sugarcane fields as well as grass turfs (lawns and golf courses), demasculinizes male gonads during developmental exposure (Hayes et al., 2011). This occurs across amphibians, reptiles, and mammals and causes an increase in the size of testicular tubules, loss of Sertoli cells, and a marked loss of germ cells. One experiment in Cuban tree frogs (*Osteopilus septentionalis*) found that atrazine did not affect the amphibian chytrid fungus *Batrachochytrium dendrobatidis* in a gut microbiome-dependent manner, however the intensity of the fungus was negatively associated with the microbial phylum Fusobacteria (Knutie et al., 2018). In zebrafish, atrazine decreased serotonin and increased inflammation in males, and affected the abundance of many genera of bacteria (Chen, L. et al., 2018b).

Glyphosate is a broad-spectrum herbicide that is the leading product for weed management by acting as a competitive inhibitor of 5-enolpyruvylshikimate-3-phosphate synthase (EPSPS), preventing the biosynthesis of aromatic amino acids and other metabolites in plants and some microorganisms that have the shikimate pathway (Motta et al., 2018). However, recent evidence suggests that glyphosate has off target effects on non-shikimate organisms. For example, chronic exposure of rat hippocampal cells to 1% Roundup® (commercial product with 0.38% glyphosate) showed decreased ^{3}H-glutamate uptake with increased glutamine uptake, indicating glutamatergic excitotoxicity (Cattani et al., 2014). Glyphosate alters the behavior of honey bees, and, interestingly, the genomes of the bee gut microbiome contain EPSPS (Motta et al., 2018). Young worker bees fed glyphosate for 5 days significantly decreased the abundance of the dominant gut microbiota species and increased their susceptibility to the opportunistic pathogen *Serratia marcescens* (Motta et al., 2018). The gut microbiome of honey bee larva fed a high concentration of glyphosate (20mg/L) had 9 taxa that were decreased relative to controls or low dose glyphosate exposures (Dai et al., 2018). Cultured gut bacteria from the gastrointestinal tracts of green turtles (*Chelonia mydas*) exposed to six different glyphosate concentrations, as well as a deionized water control, showed a decreased in four bacteria genera: *Pantoea*, *Proteus*, *Shigella*, and *Staphylococcus* (Kittle et al., 2018). Interestingly, exposing the gut bacteria of poultry *in vitro* to glyphosate demonstrated that pathogenic bacteria such as pathogenic bacteria as *Salmonella Entritidis*, *Salmonella Gallinarum*, *Salmonella Typhimurium*, *Clostridium perfringens*, and *Clostridium botulinum* are highly resistant to glyphosate, whereas beneficial bacteria *Enterococcus faecalis*, *Enterococcus faecium*, *Bacillus badius*, *Bifidobacterium adolescentis*, and *Lactobacillus spp*. were susceptible to glyphosate (Shehata et al., 2013), indicating that glyphosate could increase the risk for pathogenic diseases. Indeed, glyphosate exposure reduces the most prevalent *Enterococcus spp*. in German cattle, which can produce bacteriocins against *Clostridium botulinum* (Kruger et al., 2013).

Several studies have used rodent models to evaluate glyphosate-induced perturbations to the gut microbiome as well as possible neurotoxic associations. Mice exposed chronically to 250 or 500 mg/kg/day of glyphosate had increased anxiety and depression like behaviors as well as decreased *Corynebacterium spp.* and *Lactobacillus spp.*, indicating that key microbes could increase neurobehavioral alterations (Aitbali et al., 2018). Exposing female Sprague-Dawley rats to three doses of Roundup® increased the family *S24–7* and decreased *Lactobacillaceae*; culturable bacteria in the rat microbiome showed varying sensitivities to glyphosate, with one highly resistant *Escherichia coli* strain lacking EPSPS (Lozano et al., 2018). Another study examining the rat pups from *in utero* and developmental exposure to postnatal day 125 of glyphosate in drinking water showed an increase in *Prevotella spp.*, but a decrease in *Lactobacillus spp.* at postnatal day 31 (Mao et al., 2018). However, another study found that a diet sufficient in aromatic amino acids would prevent the antimicrobial effects of glyphosate on the rat microbiome (Nielsen et al., 2018). Overall, some bacteria that decrease from glyphosate exposure, such as *Lactobacillus spp.*, may increase the neurotoxicity of glyphosate, but further studies are warranted.

IV-7. Plant and animal toxins.

In addition to the manmade neurotoxicants, microbiome may contribute to the detoxification/toxification of the plant and animal derived toxins. For example, the neurotoxin domoic acid is produced by the diatom Pseudo-nitzschia multiseries and is responsible for the amnesic shellfish poisoning. Domoic acid exerts its neurotoxicity through activating the excitatory glutamate receptors as a structural analog to glutamate (Bates et al., 2018; Chegini and Metcalfe, 2005; Mills et al., 2016; Smith and Swoboda, 2019). Autochthonous bacteria have been suggested to contribute to the biodegradation and disposal of domoic acid, and blue mussels and soft-shell clams have been demonstrated as the unique sources of these domoic acid-utilizing bacteria (Stewart et al., 1998).

Nicotine, which is the primary active substance in tobacco, interacts with the nicotinic receptors in CNS for excitatory signaling. Studies using mouse models have shown that nicotine exposure affects the gut microbiome in a sex-dependent manner, in that there is a male gut microbiome-specific modulation of microbial pathways involved in carbohydrate metabolism, oxidative stress, and DNA repair. In addition, fecal metabolomics studies showed that multiple neurotransmitters including glutamate, GABA, and glycine, as well as the neuro-active metabolites leucine and uric acid, were altered by nicotine in both sexes (Chi et al., 2017c). This indicates that gut microbiome may at least partly contribute to nicotine's CNS effect.

Cyanide can induce tremors through neuronal calcium signaling (Johnson et al., 1986), and is enriched in secondary metabolites in bamboo. Interestingly, the bamboo-eating pandas are deficient in rhodanese, which is one of the essential cyanide-detoxifying enzymes as compared to other herbivores. Correspondingly, the gut microbiota of pandas have high proportions of Pseudomonas bacteria and enriched putative genes coding for rhodanese-like enzymes involved in cyanide degradation. This diet-driven symbiotic relationship is advantageous for the host survival during evolution (Zhu, L. et al., 2018).

IV-8. Solvents.

Solvents refer to a class of organic chemicals of varying lipophilicity and volatility classified by molecular structure and functional groups that general lack a charge and are of small molecular size. Toxicity of solvents is determined by the number of carbon atoms, saturation (number of bonds between carbon atoms), configuration of the carbon atoms, halogenation, and the presence of functional groups (Klaassen, 2013).

One of the greatest solvent exposures for most humans is ethanol through intoxicating beverages as well as from its use in household products, pharmaceuticals, industry, and gasoline additive. The metabolism of ethanol by the liver is well characterized by the formation of acetaldehyde by CYP2E1 or alcohol dehydrogenase followed by acetate by aldehyde dehydrogenase, and it is well known that chronic alcohol ingestion can induce alcoholic liver disease. Mice fed the liquid Liber-DeCarli diet with alcohol (5% v/v) for 6 weeks to induce alcoholic liver disease increased the fecal pH and increased fecal *Corynebacterium spp.* as well as the alkaline tolerant *Alcaligenes spp.* compared to mice not exposed to alcohol (Bull-Otterson et al., 2013). Supplementation with the probiotic bacterium *Lactobacillus rhamnosus* GG prevented the ethanol induced pathogenic changes. A combination of ethanol and the artificial sweetener saccharin increased Eubacteria in pregnant mice, whereas it decreased in non-pregnant mice; in pregnant mice, ethanol and saccharin increased the abundance of *Clostridium spp.* compared to ethanol and weight (Labrecque et al., 2015). Another study found that alcohol dependent mice had increased *Bifidobacterium spp.*, and metabolomics analysis revealed changes in bacteria relevant metabolism, including secondary bile acids and serotonin (Wang et al., 2018). Ethanol exposure for 3 weeks in mice induced anxiety and depression-like behaviors also increased *Adlercreutzia spp.*, *Allobaculum spp.* and *Turicibacter spp.* and decreased *Helicobacter spp.* (Xu et al., 2018). Interestingly, decreased *Adlercreutzia spp.* was positively correlated with alcohol preference and negatively correlated with anxiety-like behavior and the decreased expression of brain-derived neurotrophic factor (BDNF) and α1 subunit of γ-aminobutyric acid A receptor (Gabra1) in prefrontal cortex.

Alcohol dependent human subjects admitted to a gastroenterology ward for a 3-week detoxification and rehabilitation program had increased gut permeability by the second day of alcohol withdrawal. Alcohol dependent subjects with high gut permeability had decreased abundance of the genera *Ruminococcus*, *Faecalibacterium*, *Subdoligranulum*, *Oscillibacter*, and *Anaerofilum* as well as an increase in *Dorea* (Leclercq et al., 2014). Interestingly, increased gut permeability was negatively correlated with the reduced total number of bacteria and microbial metabolites from tryptophan metabolism, which is used for generating neurotransmission molecules such as serotonin, were low or not present in high gut permeability subjects. Mice fed a liquid diet with alcohol were protected from alcohol-induced neuroinflammation, increased small intestine and brain cytokine expression by antibiotic treatment, and antibiotics abrogated microglia activation and morphological changes in the cortex and hippocampus, demonstrating a direct connection between the gut microbiome and the CNS effects of alcohol (Lowe et al., 2018).

Associations between gut microbiome and solvents have also been investigated for formaldehyde and trichloroethylene (TCE). Formaldehyde is an irritating, gaseous solvent

that is an environmental toxic hazard found in paint, cloth, cigarette smoke and exhaust gas. Formaldehyde has many detrimental effects on various tissues including skin, eye, gonads, the gastrointestinal system and the respiratory tract, as well as the nervous system, which can cause neurobehavioral impairment and seizures (Kilburn, 1994; Tang et al., 2011). Blab-C mice exposed to formaldehyde had increased abundance of the genera *Prevotella*, *Dorea*, *Desulfovibrio*, *Adlercreutzia*, *Anaeroplasma*, *Coprococcus*, *Candidatus Arthromitus*, *Delftia*, *Lactococcus*, *and Serratia* and decreased abundance of *Bacteroides* (Guo, J. et al., 2018). TCE is a clear sweet-smelling industrial solvent with a variety of uses, including dry cleaning, film cleaning, and degreaser. TCE is a CNS depressant by inhibiting $GABA_A$ and glycine receptors (Beckstead et al., 2000; Krasowski and Harrison, 2000). Mice exposed to TCE perinatally and up to postnatal day 259 decreased the abundance of the genera *Bacteroides* and *Lactobacillus* and increased the abundance of *Bifidobactrium* (Khare et al., 2019). Overall, more research is needed to understand the contribution of the microbiome to neurotoxicity by solvents.

V. Closing remarks: microbiome as a contributor to neurotoxicity

Taken together, our review provides a comprehensive literature update regarding the role of gut microbiome in various neurological disorders, especially during chemical-induced neurotoxicity in both human subjects and animal models. Although the research in neurotioxicants and gut-brain axis is still in its early phase, we hypothesize that gut microbiome may contribute to the pathogenesis and/or resolution of neurotoxicity by 1) direct biotransformation of the xenobiotics into neuro-reactive or inactive metabolites; 2) alteration of endogenous microbial neuro-reactive metabolites, some of which may have epigenetic reprogramming potential in regulating the transcription of host genes involved in cognitive functions in brain; 3) modulating neuroinflammation by modulating intestinal barrier integrity and the systemic availability of gut-derived pro-inflammatory cytokines; and 4) regulation of mucosal immune function (Figure 1). Among various neurological disorders and chemical-induced neurotoxicity, distinct neuroactive microbial metabolites appear to be common targets, this includes decreased SCFAs and/or decreased abundance of SCFA-producing bacteria in AD mouse models (Zhang et al., 2017), anorexia nervosa patients (Borgo et al., 2017; Morita et al., 2015), PD patients (Unger et al., 2016), ASD patients (De Angelis et al., 2013; Kang et al., 2013), as well as ionic gold (Kase et al., 1987) and permethrin/pyridostigmine bromide co-exposed mice (Seth et al., 2018). Conversely, SCFA supplementation has been shown to improve AD (Govindarajan et al., 2011; Vinolo et al., 2011), and restore permethrin-induced gut dysbiosis, stalls microbiome-induced GI inflammation in Gulf War illness mouse model (Seth et al., 2018). This is likely contributed by the HDAC inhibitor and anti-inflammation properties of SCFAs (Bourassa et al., 2016; Matt et al., 2018; Vinolo et al., 2011). Tryptpohan metabolism is another important common target in neurotoxicity, as it is dysregulated in ASD (Golubeva et al., 2017), MDD (Kazemi et al., 2018; Rudzki et al., 2019), alcohol addition (Leclercq et al., 2014), as well as manganese- and organophosphate-induced neurotoxicity (Chi et al., 2017b; Slotkin et al., 2008; Timofeeva et al., 2008; Waclawikova and El Aidy, 2018). These common targets should be especially focused on as they may represent common signaling pathways that can be harnessed therapeutically to mitigate neurotoxicity.

In the endeavor to move forward the research on gut-brain axis and neurotoxicity, we propose that it will be important to consider the following aspects:

1) Beyond associations: more mechanistic investigations are needed *in vitro* and at the single microbial species resolution to establish the causality.

A combination of research tools including anaerobic culture of bacteria, GF mice, fecal transplant/single strain inoculations, metabolomics, as well as biochemical and behavioral assessment of CNS functions, will likely lead to a more thorough understanding of the exact molecular mechanisms of gut microbiota-mediated regulation of CNS functions. For example, Dr. Elaine Hsiao's group demonstrated how the ketogenic diet exerts its anti-seizure effects in mice through modulating the gut microbiota by initially using a multi-omics approach of 16S rDNA sequencing and metabolomics followed by identification of key bacteria that mitigate seizures (Olson et al., 2018). The ketogenic diet promoted the enrichment of the genera *Akkermansia* and *Parabacteroides* in the intestine and correlated with reduction in systemic gamma-glutamylated amino acids and increased hippocampal GABA/glutamate levels. The dependency of gut microbiota in ketogenic diet mediated anti-seizure effect was confirmed using antibiotic-exposed mice and GF mice, inoculation of specific bacteria (*Akkermansia* and *Parabacteroides)*, and fecal microbiome transfer (Olson et al., 2018). Overall, this study demonstrated which bacteria modified by ketogenic diet mechanistically contributed to seizure protection in mice.

The SHIME system, or a similar microbial culturing method, is another tool that could be used to study the specific effects of chemical exposures on bacteria and understand how the chemicals may alter gut microbiome composition in humans. Because the system uses a dynamic series of six compartments that can mimic the intestines (Joly et al., 2013; Requile et al., 2018), some bacteria that have not be cultured by traditional methods may colonize with the system. Furthermore, the bacteria cultured before and after exposure could be used to colonize GF mice to elucidate a microbiome dependent effect in a paradigm such that exposure causes a gut dysbiosis which leads to neurotoxicity. The SHIME system was used to characterize the effect of exposures on the microbiome, including arsenic (Yin et al., 2017; Yin et al., 2015; Yu et al., 2016) and chlorpyrifos (Joly et al., 2013; Requile et al., 2018; Reygner et al., 2016a).

In general, an obstacle to study the role of intestinal bacteria using single strain anaerobic cultures is that a substantial number of the intestinal bacteria are not culturable *in vitro* (Lagier et al., 2015; Lagkouvardos et al., 2017). This is partly because the artificial media may lack key growth factors that are provided by other symbiotic bacteria in the gut (D'Onofrio et al., 2010; Fenn et al., 2017). Co-cultures of multiple microbial species may be the solution to this problem, and this method has been shown to be successful in characterizing GABA-modulating bacteria in the human gut (Strandwitz et al., 2019). Because microbes live in a symbiotic environment in the gut, metabolites produced by one microbe may serve as important substrates for the function of another microbe. Conversely, antagonistic microbes can compete with each other for the same nutrient niche and may inhibit a particular signaling pathway under physiological or pathophysiological conditions (Das et al., 2018). Therefore, in the effort to determine the mechanistic roles of microbes at

single species resolution, it is important to perform co-culture experiments to investigate the microbe-microbe interactions, and identify key microbial metabolites in the context of microbial networks that contribute to the pathogenesis of neurological diseases. In addition, it is important to include host enterocytes in the co-culturing system, so as to determine the interactions between distinct microbes and host receptors (Sadaghian Sadabad et al., 2015).

In addition, steady-state pre-rRNA analysis, which quantifies the ribosomal RNA precursors instead of mature 16S rDNA, has been shown to be a more promising culture-independent tool to assess the active growth status of the bacteria. Pre-rRNA is rapidly replenished when growth-limited bacteria encounter a more favorable growth environment, and such changes can occur only in viable bacteria but not in dead cells or with free nucleic acids. Pre-rRNAs also appear to be a more sensitive biomarker to environmental stress as compared to the mature rDNA signals (Cangelosi and Brabant, 1997; Cangelosi and Meschke, 2014; Mackow and Chang, 1985; Oerther et al., 2000; Srivastava and Schlessinger, 1990). Lastly, taking the advantage of the CRISPR-Cas9 gene-editing system, one could engineer individual intestinal bacteria to investigate the necessity of the microbial genes at single species resolution (Mimee et al., 2015).

2) Beyond 16S rDNA survey: investigating microbial genes and neuroactive microbial metabolites to further decipher the bacterial functions.

As reviewed in Tables 1 and 2, a substantial amount of research in gut microbiome and neurological disorders has utilized 16S rDNA gene sequencing, which has provided important and valuable information regarding what taxa are differentially regulated during the progression of diseases. However, 16S rDNA gene sequencing often does not resolve taxonomy past the genus level and provides only moderately accurate predictions of the functional changes. Deep whole-metagenome shotgun sequencing, as well as a more cost-effective approach, namely shallow shotgun metagenomic sequencing, are highly recommended alternatives for high resolution taxonomic and functional microbiome analysis (Hillmann et al., 2018). In addition, we believe that more research using metatranscriptomics (Bashiardes et al., 2016) and metaproteomics (Mills et al., 2019) are needed to further characterize the gut microbiome functions beyond DNA level. Computational tools for functional predictions of the microbiome, such as FishTaco and AGORA (Magnusdottir et al., 2017; Manor and Borenstein, 2017), followed by wet lab validations using metabolomics approach (Daliri et al., 2017), will also provide further mechanistic insights into further understanding the gut-brain axis in neurotoxicity.

Specifically, building on the known neuroactive microbial metabolites that contribute to the pathogenesis and/or mitigation of neurotoxicity, it is important to determine the regulation of these microbial genes that are responsible for the production of these metabolites. As summarized in this review, SCFAs are commonly reduced in AD mouse models (Zhang et al., 2017), anorexia nervosa patients (Borgo et al., 2017; Morita et al., 2015), PD patients (Unger et al., 2016); whereas decreased SCFA-producing bacteria were also observed in intestines of ASD patients (De Angelis et al., 2013; Kang et al., 2013), ionic gold exposed mice (Kase et al., 1987), permethrin and pyridostigmine bromide co-exposed mice (Seth et al., 2018). Dysregulation in microbial and/or host tryptophan metabolism was found

associated linking to ASD behavior (Golubeva et al., 2017); MDD (Kazemi et al., 2018; Rudzki et al., 2019), alcohol addition (Leclercq et al., 2014), as well as manganese- and organophosphate-induced neurotoxicities (Chi et al., 2017b; Slotkin et al., 2008; Timofeeva et al., 2008; Waclawikova and El Aidy, 2018). It is especially important to focus on the neuroactive metabolites that are commonly regulated in neurological disorders of various etiology, such as SCFAs and tryptophan microbial metabolites.

3) Beyond intestinal bacteria: characterizing the involvement of other microorganisms in neurotoxicity

Although most of the current endeavors in exploring the gut microbiome have focused on intestinal bacteria, other microorganisms are important for neurodegenerative diseases and may also provide alternative therapeutic options. These other microorganisms that could be essential to the normal function of the host or contribute to pathogencity of diseases include fungi, porotozoa, and viruses (Barko et al., 2018). Fungi have been detected in different brain regions in Alzheimer's disease patients (Alonso et al., 2018; Pisa et al., 2015), as well as in patients with amyotrophic lateral sclerosis (Alonso et al., 2017). One hypothesis is that these fungi are of gut origin and may be a result of gut leakage. Regarding viruses, it is not known what viruses in the gut microbiome may be beneficial to host health, however bacteriophage therapy may be method to alter the gut microbiome. The gut microbiome of gnotobiotic mice colonized with known human gut bacteria was modulated by lytic phages that shifted the gut microbiome composition and the gut metabolome, suggesting that bacteriophage could be used to modulate the microbiome (Hsu et al., 2019). Indeed, intravenous treatment with engineered phages was used to treat a cystic fibrosis patient with a drug-resistant strain of *Mycobacterium abscessus* (Dedrick et al., 2019). More research is needed in this field to further characterize the sources, types, and mechanistic involvement of these microorganisms during various types of neurological diseases. The bioavailability of gut-derived microorganisms and microbial products should also be assessed when considering the presence of the blood-brain barrier.

4) Beyond early-life exposure: epigenetic reprogramming via microbial metabolites.

Early-life exposure to environmental chemicals has been shown to be an important contributing factor for developmental origins of human diseases. Along those lines, early-life induced dysbiosis may also predispose the host organism to delayed onset of adverse health outcomes including neurodegenerative diseases. There is a critical time window early in life to target the microbiome and modulate late-onset of Alzheimer's disease, because acute antibiotic-treatment in perinatal period resulted in long-term alterations of gut microbiota (especially Lachnospiraceae and S24–7) and reduction in brain Aβ deposition, as well as reduced inflammatory signaling in serum and brain of aged AD mice (Minter et al., 2017). Neuroactive microbial metabolites, such as SCFAs which have anti-inflammatory HDAC inhibitor properties, may be beneficial against the pathogenesis of AD (Govindarajan et al., 2011; Vinolo et al., 2011). Therefore, linking gut microbiome and metabolome to host epigenome and inflammasome is an exciting approach to investigate the remote-sensing mechanisms between the gut and brain.

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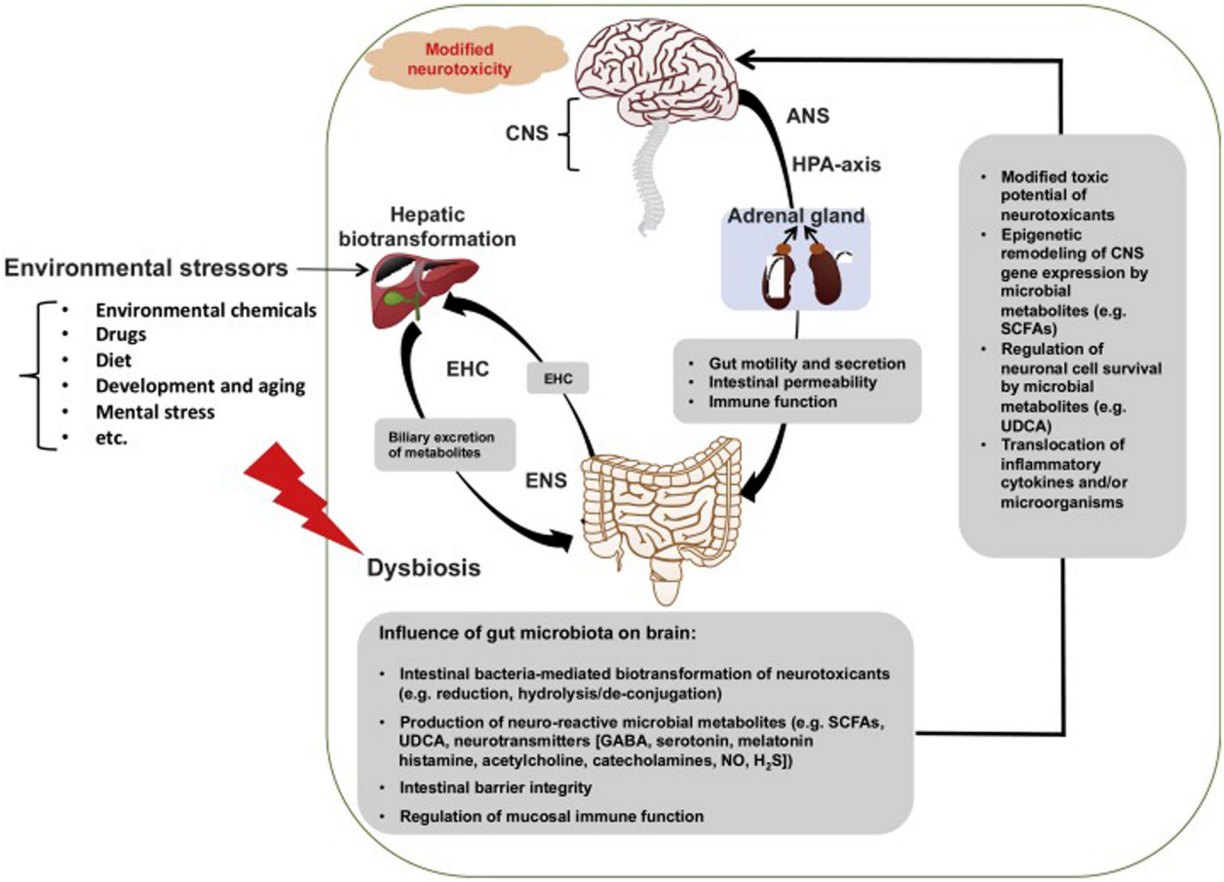

Figure 1.
An illustration of the gut-brain axis in environmental stressor induced neurotoxicity.

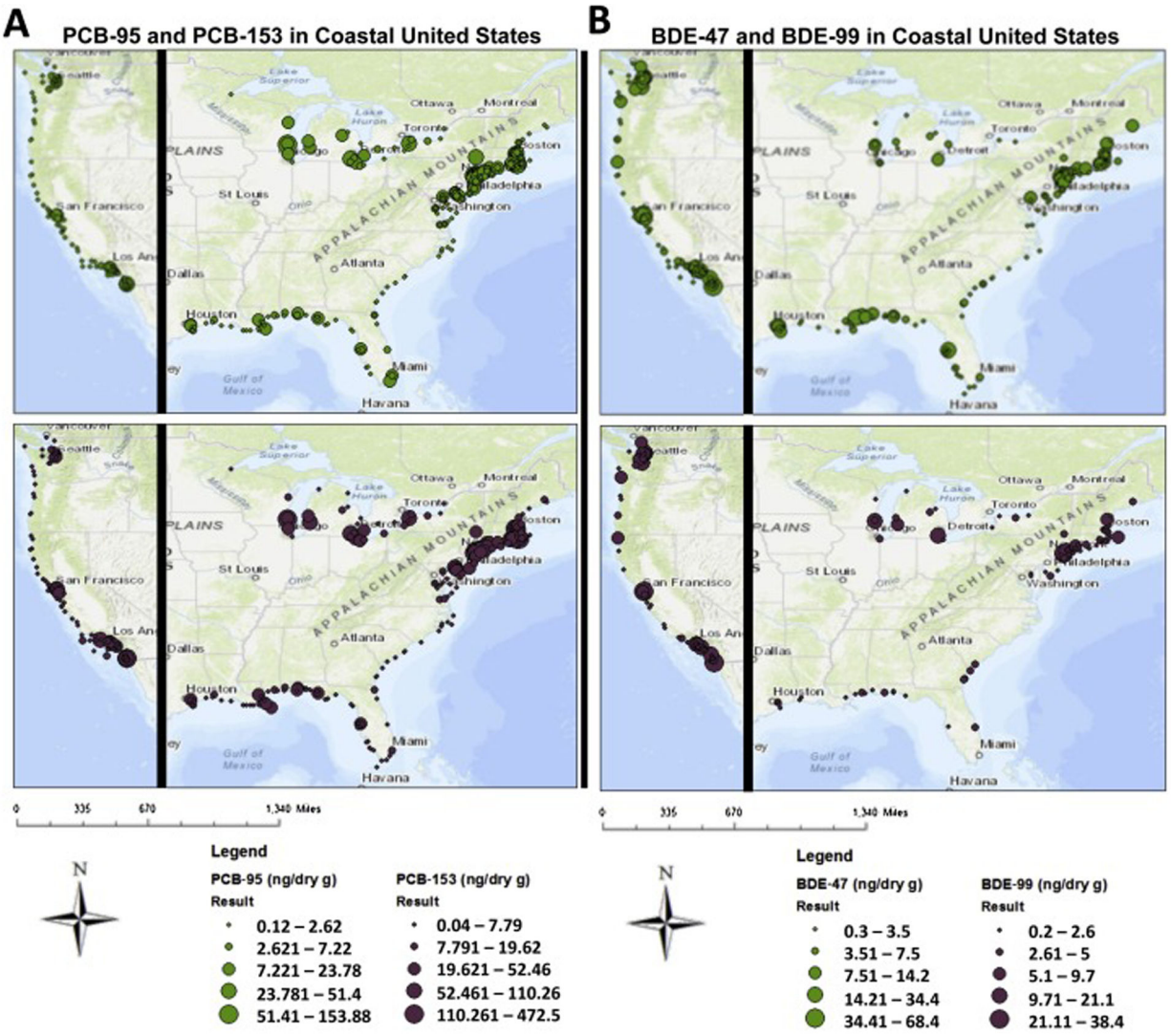

Figure 2.

Collection sites and concentrations of BDE-47, BDE-99, PCB-95, PCB-153, lead, and manganese in bivalves collected from the coastal United States. (A) Green circles indicate BDE-47 sampling sites while purple circles correspond to BDE-99 sampling sites in bivalves with size corresponding to concentration (ng/dry g). (B) Green circles indicate PCB-95 sampling sites while purple circles correspond to PCB-153 sampling sites in bivalves with size corresponding to concentration (ng/dry g). (C) Green circles indicate lead sampling sites while purple circles correspond to manganese sampling sites in bivalves with size corresponding to concentration (μg/dry g).

Table 1.

Studies investigating neurological diseases in the gut-brain axis.

Disease	Model	Bacteria influence	Source
ADHD	Human adolescents and adults	Association	(Aarts et al., 2017)
	Human children	Association (biomarker)	(Jiang et al., 2018)
	Humans: juvenile males	Association (diversity; biomarker)	(Prehn-Kristensen et al., 2018)
	Humans: cesarean delivery or antibiotic use during first two years of life	No association	(Axelsson etal., 2019a)
Alzheimer's disease	Mice	Association (diversity)	(Hoffman et al., 2017)
	Artificial Aβ aggregation assays	Inverse association with SCFAs	(Ho et al., 2018)
Anorexia nervosa	Human adult females	Association	(Borgo et al., 2017; Kleiman et al., 2015; Mack et al., 2016; Morita et al., 2015; Morkl et al., 2017)
	Mice	Association	(Chen et al., 2016)
Autism	Human children	No association	(Gondalia et al., 2012)
	Human children	Association	(Coretti et al., 2018; De Angelis et al., 2013; Finegold et al., 2010; Hicks et al., 2018; Kang et al., 2013; Liu et al., 2019; Pulikkan et al., 2018; Qiao et al., 2018; Rose et al., 2018; Son et al., 2015; Wang, M. et al., 2019)
	Mice valproic acid-induced	Association	(de Theije et al., 2014)
	BTBR T^{+}ltpr3^{tf}/J mouse model of ASD	Association	(Coretti et al., 2017; Golubeva et al., 2017)
	Juvenile hamsters clindamycin and propionic acid induced	Mechanistic	(El-Ansary et al., 2018)
	Shank3-null mice	Mechanistic	(Tabouy et al., 2018)
	Rat valproic acid-induced	Association (biomarker)	(Liu et al., 2018)
Autism and antibiotics	Human children in Manitoba, Canada or Denmark	No association	(Axelsson et al., 2019b; Hamad et al., 2018)
Autism and Vitamin A	Human children with autism	Association	(Liu, J. et al., 2017)
Behavior - generic germ-free	Germ-free mice	Association	(Arentsen et al., 2015; Lu et al., 2018; Neufeld et al., 2011; Sudo et al., 2004)
	Germ-free mice	Mechanistic	(Diaz Heijtz et al., 2011)
	Germ-free, stress-sensitive rats	Association	(Crumeyrolle-Arias et al., 2014)
	Antibiotic-exposed mice	Association	(Desbonnet et al., 2015)
Bipolar	Human adults	Association	(Evans et al., 2017; Painold et al., 2018; Vinberg et al., 2019)
	Human adults	Mechanistic	(Painold et al., 2018)
Depression	Mice	Mechanistic	(Sun, J. et al., 2018; Zheng et al., 2016)30521978 (Huang et al., 2019)
	Rats	Association	(Tillmann et al., 2018; Yu et al., 2017)

Disease	Model	Bacteria influence	Source
	Rats	Mechanistic	(Abildgaard et al., 2017; Kelly et al., 2016)
	Human adults	Association	(Aizawa et al., 2016; Chen, J.J. et al., 2018; Chen, Z. et al., 2018; Jiang et al., 2015; Lurie et al., 2015; Naseribafrouei et al., 2014)
	Human adults	Mechanistic	(Kazemi et al., 2018; Miyaoka et al., 2018; Rudzki et al., 2019)
Parkinson's disease	Human adults	Association	(Hill-Burns et al., 2017; Unger et al., 2016)
	Mice	Mechanistic	(Sampson et al., 2016)
Postpartum depression	Adult women	Mechanistic	(Slykerman et al., 2017)
	Pregnant women	Association	(Murphy et al., 2018)
PTSD	Humans	Association	(Hemmings et al., 2017)
	Male mice	Association	(Gautam et al., 2015; Gautam et al., 2018)
Schizophrenia	Rats	Association	(Dunphy-Doherty et al., 2018; Pyndt Jorgensen et al., 2015)
	Humans	Association	(Castro-Nallar et al., 2015; Flowers et al., 2019; Nagamine et al., 2018; Nguyen et al., 2019; Olde Loohuis et al., 2018; Shen et al., 2018)
	Humans	Mechanistic	(Okubo et al., 2019)
	Mice	Mechanistic	(Zheng et al., 2019)

Table 2.

Studies investigating neurotoxicants and microbiome.

Category	Toxicant	Model	Dose or exposure	End point and bacteria result	Source
Air pollution	$PM_{2.5}$	Mouse (8–12 weeks old)	135.4 ± 6.4 mg/m^3 8 hours for 5 days/ week for 3 weeks	Increased genera, as well as alpha and beta diversity	(Mutlu et al., 2018)
	PM_{10}	Mouse (6–8 weeks old)	18 μg/g/day (oral gavage)	Altered short chain fatty acid concentrations and microbial composition	(Kish et al., 2013)
Dietary and herbal medicine	Fructooligosaccharides	Rat (adults given 100 mg/kg/d d-galactose i.p. for inducing AD)	100 mg/kg/d (oral gavage)	Maintains gut microbiota diversity while improving neurological endpoints	(Chen et al., 2017)
	Ketogenic diet	Mouse (adult 6-Hz induced seizure model of refractory epilepsy)	6:1 fat:protein ketogenic diet (ad *libitum*)	Increased hippocampal GABA/glutamate levels mechanistically by *Akkermansia* and *Parabacteroides*	(Olson et al., 2018)
Drugs	Amiodarone	Rat (adult)	Probiotic: 1.5 × 109 CFU/dose once daily for 7 days Amiodarone: 50 mg/kg (single oral dose)	*E. coli* Nissle 1917 increased the bioavailability whereas L. casei DN-114 001 delayed max plasma concentration	(Matuskova et al., 2017; Matuskova et al., 2014)
	Chemotherapeutics	Bacteria (*in vitro*)	Variable—dose-response relatationship (screens to identify bacteria susceptible to chemotherapeutics)	Lactic acid bacteria and bifidobacteria may be susceptible whereas other bacteria may affect efficacy	(Florez et al., 2016; Lehouritis et al., 2015)
	Cisplatin	Mouse (8–12 weeks)	Cisplatin: 10mg/kg Probiotic: healthy donor fecal pellet or 2×10^8 Ruminococcus gnavus	Probiotic ameliorated intestinal toxicity and systemic inflammation of cisplatin	(Perales-Puchalt et al., 2018)
	Disulfiram	Bacteria (*in vitro*)	Variable (disulfiram and metabolites)	Antimicrobial activity against gram-positive bacteria	(Frazier et al., 2019; Long, 2017; Sheppard et al., 2018)
	Doxorubicin	Mouse (8–10-week-old females)	20 mg/kg by i.p.	Enteric injury (crypt depth, crypt number, and proliferative cell number) is dependent on presence of bacteria	(Rigby et al., 2016)
		Bacteria (*in vitro*)	150 μg/mL	Deglycosylation of doxorubicin reduces toxicity	(Yan et al., 2018)
		Mouse (7–10-week-old females)	10 mg/kg by i.p.	Pre-treatment with pectin (1.5 mg per day orally) protected against ileitis independent of SCFAs	(Sahasrabudhe et al., 2018)
	Lithium, valproate and aripiprazole	Rat (adult)	Variable	Increased microbial species richness and diversity; some antimicrobial activity	(Cussotto et al., 2018)
	Metronidazole	Rat (adult males)	1 mg/ml in drinking water for 1 week	Increased in *Bifidobacterium spp.* and *Enterobacteriaceae* and increased mucosal thickness	(Pelissier et al., 2010)

Category	Toxicant	Model	Dose or exposure	End point and bacteria result	Source
		Mouse (8-week-old males)	30 mg/kg by i.p.	Decreased Firmicutes and order Clostridiales; increased Proteobacteria, Turicibacterales and Enterobacteriales; PD-like effects abrogated by FMT	(Sun, M.F. et al., 2018)
	MPTP	Mouse (male and/or female adults, WT and metabotropic flutamate receptors knockout)	18 mg/kg 2 times per week for 5 weeks 10 mg/kg for 5 days, rest 2 days, 20 mg/kg for 5 days by i.p.	Altered microbiome composition; Gender- and genotype-specific results; associations between microbiome diversity and sensorimotor performance	(Lai et al., 2018; Torres et al., 2018)
	Nano-encapsulated doxorubicin and paclitaxel	Mouse (8-week-old males)	12.93 μmol/kg	Altered microbial activity indicated by levels of hippurate and indoxyl sulfate	(Song et al., 2015)
	Nitrofurantoin	Human (adults)	100 mg twice per day	Decreased Clostridium sp. and increased Faecalibacterium sp.	(Stewardson et al.,2015; Vervoort et al., 2015)
Metals	Arsenic	Mouse (8-week-old males and females)	100 ppb sodium arsenite for 13 weeks Up to 250 ppb Antibiotic-treated for 3 days then exposed up to 1 ppm arsenic in drinking water for 2 weeks (females only)	Altered gene abundances for genes involved in carbohydrate metabolism, pyruvate fermentation, short-chain fatty acid synthesis, and starch utilization Arsenic eroded bacterial biofilms adjacent to the mucosa 1 ppm arsenic did not alter gut microbiome	(Chi et al., 2016; Chi et al., 2017a; Chi et al., 2019; Dheer et al., 2015; Lu et al., 2014)
		Mouse (7–13-week-old males and females)	25 and 100 ppm sodium arsenate	Antibiotic-treated and GF mice accumulate more arsenic than controls; human fecal transplants protect mice lacking the arsenic detoxification enzyme from arsenic-induced mortality, but may depend on Faecalibacterium spp.	(Coryell et al., 2018)
		Earthworm (*Lumbricus rubellus*)	Devon Great Consols (DGC) mine site	Slight trend for an association between worm microbiome diversity and arsenic contamination	(Pass et al., 2015)
		Human (*in vitro*; SHIME)	Soil arsenic concentrations (varies) 100μg/L As, 600 μg/L As, 600 μg/L As and 0.1 mg/L Fe, 600 μg/L As and 0.3 mg/L Fe, and 600 μg/L and As+3 mg/L Fe	Bioaccessibility in the Arsenic was 1.8–2.8 times more bioaccessible in the colon than in the small intestinal phase Iron decreased bioaccessibiility of arsenic with increased arsenic methylation;	(Yin et al., 2015; Yu et al., 2016)
		Human (*in vitro*; Caco-2 cells)	Soil arsenic samples ranging from 15.5 to 3225.6 mg/kg	Gut microbiota can directly release soil arsenic; arsenic in colon is digested more quickly than in soil	(Yin et al., 2017)
		Human	Children: high group (218.8 μg/L in drinking water) and low group (1.7 μg/L in drinking water) Infants at 6 weeks of age	Children: high arsenic group had increased Gammaproteobacteria class, Enterobacteriales order, and *Enterobacteriaceae* family Infants: 8 genera were enriched with higher arsenic exposure, whereas 15 genera	(Dong et al., 2017)(Hoen et al.,2018)(Wu et al., 2019)

Category	Toxicant	Model	Dose or exposure	End point and bacteria result	Source
			Adult men and women	were decreased; changes were associated with males, but not females Time-weighted urinary arsenic associated with order Campylobacterales and the genera *Anaerostipes* and *Faecalibacterium*	
		Zebrafish (larva)	10, 50, and 100 ppb for 20 days	Increased the genera *Acinetobacter, Sediminibacterium*, and *Janthinobacterium*; decreased the genera *Bdellovibrio* and *Pseudomonas*	(Dahan et al., 2018)
	Copper	Broiler chicken (Start from Day 0 as chicks)	8 or 187.5 mg/kg of Cu from Cu Sul or 187.5 mg/kg of Cu from TBCC	No affect on performance by Cu source or concentration	(Pang et al., 2009)
		Holstein-Friesian calves (Dairy cows; 7 month old males)	3g/100 L of copper supplementation as cupric sulphate in drinking water for 75 days	Increased microbial alpha diversity in rumen; altered bacteria *S24–7, Planctomycetaceae p-1088-a5* gut group, and *Azospira spp.*	(Biscarini et al., 2018)
	Gold	Mouse (7–8-week-old males)	Up to 25 μg gold/kg bodyweight for 8 7 different types of gold nanoparticles for 8 days during and after 5-day dextran sodium sulfate exposure	5 nm/Citrate and Au-5 nm/ polyvinylpyrrolidone attenuated colonic and systemic inflammation; gold nanoparticles decreased alpha diversity;	(Zhu, S. et al., 2018)
	Lead	Mouse	8 week old females: 10 ppm for 13 weeks; 32 ppm to dams in drinking water 2 weeks prior to breeding and up to 40 weeks of age for pups 6-week-old males and females: 0.01, 0.03, or 0.1 mg/L Pbfor15 weeks	Majority of bacteria decreased following lead exposure; Cultivable aeobes decreased and anaerobes increased; at highest exposure, decreased Firmicutes and increased Bacteroidetes and Proteobacteria	(Gao et al., 2017c; Wu et al., 2016; Xia, J. et al.,2018a)
		Zebrafish (adult males)	10 and 30 μg/L for 7 days	52 microbes altered by 30 ug/L PB group; altered metabolites in pathways for glucose and lipid metabolism, amino acid metabolism, nucleotide metabolism	(Xia, J. et al., 2018b)
		Carp (*Cyprinus carpio*; 105 days old)	1 mg/L	Pb decreased the expressions of pro-inflammatory cytokines; Lactobacillus reuteri P16 decreased mortality, improved the growth performance, and abrogated changes in gene expression	(Giri et al., 2018)
	Magnesium	Mouse (8-week-old males)	Standard diet with 500 mg Mg/kg food and magnesium deficient diet with 50 mg Mg/kg food for 6 weeks	Increased depressive-like behavior with magnesium deficiency; the gut microbiome was altered by magnesium deficiency and was positively correlated with hippocampal interleukin-6	(Winther et al., 2015)
	Manganese	Mouse (8-week-old males and females)	100 ppm in drinking water for 13 weeks	Altered tmicrobial tryptophan and phenylalanine biosynthesis pathways; bacteria of male mice had altered GABA/ putrescine metabolism	(Chi et al., 2017b)

Category	Toxicant	Model	Dose or exposure	End point and bacteria result	Source
	Mercury	Mummichog (*Fundulus heteroclitus*)	Total mercury in food: 0.08, 24.4, or 131 μg/g dry weight for 15 days	Microbial Hg resistance gene mercuric reductase 8 times higher in fish at Hg contamination site	(Lloyd et al., 2016)
	Methylmercury	Human (36–39 weeks pregnant)	Hair: 57 ng total Hg/g hair; Stool: 150(2.1–810) ng total mercury /g stool; Cord blood: 0.23 (0.061–0.73) μg MeHg/L cord blood	17 genera were correlated with mercury concentration in stool or hair	(Rothenberg et al., 2016)
		Fathead minnow and mouse	Minnow: 0.02, 0.72, 0.87, or 5.50 μg/g, mercury in food twice daily for 30 days Mice: 0.02 μg/g, 0.43 μg/g, or 4.39 ± 0.57 μg/g mercury in food twice daily for 30 days	Minnow gut microbiome adapted to detoxify MeHg; Mouse midbrain L-glutamine, O-phosphatidylcholine, dopamine, tagatose, hydroquinone, L-ascorbic acid, inosine 5-monophosphate, and uracil decreased	(Bridges et al., 2018)
		Bacteria (*in vitro*; fresh human fecal samples in anaerobic chamber)	10 ng/g monomethylmerc ury and 1 ng/g mercury for 0, 12, 24, 36, and 48 hours	Monomethylmercury concentration decreased under a balanced or protein rich diet, but not a carbohydrate rich diet	(Guo, G. et al., 2018)
	Arsenic and zinc	Mouse (4-week-old females)	Zinc-adequate diet with 0, 50, or 500 ppb arsenic or zinc-deficient diet with 0, 50, or 500 ppb arsenic And drinking water with 0, 50, or 500 ppb sodium arsenite for 6 weeks	No interaction between arsenic exposure and zinc restriction; plasma zinc concentration was positively correlated with the genera *Shewanella, Rheinheimera*, and *Bifidobacterium*	(Gaulke et al., 2018)
	Arsenic, cadmium, cobalt, chromium, and nickel	Rat (adults)	15, 22, or 31 mg/kg/day sodium arsenite; 35, 54, or 85 mg/kg/day cadmium chloride; 44, 62, or 88 mg/kg/day sodium dichromate, 27, 47, or 82 mg/kg/day cobalt chloride, or 177, 232, or 300 mg/kg/day nickel chloride for 5 days	47 genera were affected by at least one metal exposure; nickel uniquely altered 25 genera; bacteria with higher iron importing genes were increased by arsenic and nickel	(Richardson et al., 2018)
	Lead and cadmium	Mouse (6-week-old females)	For 8 weeks: Cadmium: 20 or 100 ppm Lead: 100 or 500 ppm	Decreased *Lachnospiraceae* and increased *Lactobacillaceae* and *Erysipelotrichaceae*	(Breton et al., 2013)
	Mercury and copper	Mouse (8-week-old females)	5 mg/kg copper, 2 mg/kg mercury, or 2.5 mg/kg copper and 1 mg/kg mercury	Copper decreased *Rikenella spp.*, *Jeotgailcoccus spp.*, and *Staphylococcus spp.*; mercury decreased *Rikenella spp, Jeotgailcoccus spp*, and *Staphylococcus spp*	(Ruan et al., 2018)
	Mercury, lead, arsenic, and cadmium	Humans (children and pregnant women)	Lead (μg/L): 22.6 or 47.1 Mercury (nmol/L): 8.8 and 9.5 Arsenic (nmol/L): 3.0 and 6.5 Cadmium (nmol/L): 1.1 and 1.2)	Lactobacillus rhamnosus GR-1 protected against mercury and arsenic blood levels in pregnant women; Increased blood lead levels was associated with increased	(Bisanz et al., 2014)

Category	Toxicant	Model	Dose or exposure	End point and bacteria result	Source
				Succinivibrionaceae and Gammaproteobacteria	
	Lead and PCBs	Human (males and females age 60–84)	Lead geometric mean of 2.17 μg/dL; many PCBs; geometric mean range of individual PCBs in blood of 7.86–66.99 ng/g lipid	Increased PCB-146 and lead concentrations result in lower Digit Symbol Coding Test of the Weschler Adult Intelligence Scale	(Przybyla et al., 2017)
Noise	Noise	Mouse (3-month-old male senescence-accelerated mouse prone 8)	<40 (background), 88, or 98 decibels for 30 days	Cognitive impairment and Aβ accumulation; changes similar to aged mice; decreased gut microbiota diversity; fecal transplant of noised-exposed mice induced epithelial integrity impairment and Aβ accumulation to unexposed mice	(Cui et al., 2018)
Environmental chemicals - PBDEs	BDE-47 and BDE-99	Mouse (9-week-old male CV and GF)	100 μmol/kg for 4 days	Lack of gut microbiome altered PBDE metabolite profiles; increased *Akkermansia muciniphila* and *Allobaculum spp.*; BDE-99 increased unconjugated bile acids	(Li et al., 2018; Li et al., 2017)
	DE-71	Zebrafish (male and female adult)	5.0 ng/L for 7 days	Decreased *Mycoplasma spp., Ruminiclostridium spp., unclassified Firmicutes sensu stricto spp.*, and *Fusobacterium spp.*; disrupted intestinal neural signaling, epithelial barrier integrity in males	(Chen, L. et al., 2018a)
Environmental chemicals - PCBs	PCB-126	Mouse (8-week-old male $Ldlr^{-/-}$)	1 μmol/kg at weeks 2 and 4 of a 12 week study	Decreased *S24.7*, *Clostridiales, Bifidobacterium spp., Ruminococcus spp., Oscillospira spp.*, and *Lactobacillus spp.* and increased *Akkermansia spp.*; positive associations between *Bifidobacterium spp.* and GLP-1, as well as *Akkermansia spp.* and fasting blood glucose	(Petriello et al., 2018)
	Multiple	Mouse	Adult females: Varied up to 50 mg/kg 11–13 month old males with voluntary exercise 5 weeks prior: 150 μmol/kg	*Parasutterella, Ruminococcus, Prevotellaceae_UCG*-001, *Alloprevotella* and *Parabacteroides* were decreased by PCBs; exercise attenuated PCB-induced changes in gut microbiome	(Chi et al., 2018; Choi et al., 2013)
Pesticide - Carbamates	Aldicarb	Mouse (8-week-old males)	2 ppm for 13 weeks in drinking water	Increased genes involved in virulence, adhesion, bacteriocins, antioxidant defense, protein degradation, DNA repair	(Gao et al., 2018b)
	Many	Bacteria from rumen of Holstein dairy cows (*in vitro*)	Concentration varied; screened for bacteria that degrade carbamates through esterase activity	26 isolates had esterase activity and degraded at least 1 polyurethane and pesticide carbamate	(Ufarte et al., 2017)
Pesticide - Neonicotinoid	Imidacloprid	Fruit fly (*Drosophila melanogaster*, adults and larva)	10, 50, and 100 μM in food	Increased *Acetobacter spp.* and *Lactobacillus spp.*; survival decreased with co-exposure to bacterial infection or heat stress	(Daisley et al., 2017)

Category	Toxicant	Model	Dose or exposure	End point and bacteria result	Source
		Honey bee (*Apis mellifera*; adults)	500 μg/liter imidacloprid suspended in sterilized sucrose syrup for 3 days	Little or no impact on the gut microbiome of adult worker bees	(Raymann et al., 2018)
Pesticide - Organochlorine	p, p'-DDE and β-HCH	Mouse (adult males)	p, p'-DDE: 1 mg/kg body weight/day β-HCH: 10mg/kg body weight/day	Both chemicals decreased the genera *Parabacteroides, Prevotella, Bacteroides, Clostridium XlVa and Clostridium IV* and increased *Barnesiella, Alloprevotella, Oscillibacter, Lactobacillus, Parasutterella* and *Akkermansia*	(Liu, Q. etal., 2017)
Pesticide - Organophosphate	Azinphos-methyl	Human	0.021 to 6.192 ng azinphos-methyl/g blood serum	Decreased *Streptococcus, Micrococcineae, Gemella, Haemophilus, Halomonas, Actinomycineae*, and *Granulicatella*	(Stanaway et al., 2017)
	Chlorpyrifos	Rat and human (*in vitro*; SHIME)	SHIME: 1 mg/day for 30 days Rat dams and pups: 1 mg/kg/day from gestation till 60 days of age	SHIME: increased *Enterococcus spp.* and *Bacteroides spp.*; decreased *Lactobacillus spp.* and *Bifidobacterium spp.* Rats: Decreased *Lactobacillus spp.* and *Bifidobacterium spp.*	(Joly et al., 2013)
		Rat	Adult males exposed to 0.3 or 3 mg/kg/day for 9 weeks Dams exposed orally from gestation to weaning and pups exposed thereafter at 1 or 3.5 mg/kg/day Dams exposed orally from gestation to weaning and pups exposed thereafter at 1 or 5 mg/kg/day	*Sutterella spp.* consistently enriched regardless of diet (normal or high-fat) In ileum, increased *Enterococcus spp., Clostridium spp., Staphylococcus spp.*, and *Bacteroides spp.*; Decreased *Bifidobacterium spp.* in ileum and colon Inulin supplementation in drinking water abrogated chlorpyrifos-induced metabolic disorders in adults exposed *in utero*	(Fang et al., 2018; Joly Condette et al., 2015; Reygner et al., 2016b)
		Mouse (10-week-old male mice)	1 mg/kg/day for 30 days	Increase lipopolysaccharide and diamine oxidase in the serum; increased *Lactobacillaceae* and decreased *Bacteroidaceae*	(Zhao et al., 2016)
		Human (in vitro; SHIME)	0.35 and 1 mg/mL working solution	inulin co-treatment partially reversed dysbiosis and inhibited pro-inflammatory signaling when effluent was applied to Caco-2/TC7 intestinal cells; Increased in *Enterobacteriaceae, Bacteroides spp.* and Clostridia	(Requile et al., 2018; Reygner et al., 2016a)
		Diamondback moth larva (*Plutella xylostella*)	Cabbage leaves dipped in 50 g/L solution for 10 minutes	Larva resistant to insecticides had increased levels of Lactobacillales order; Isolated from P. *xylostella, Enterococcus sp.* increased, *Serratia sp.* decreased, and *Enterobacter sp.* had not effect on insecticide resistance	(Xia, X. et al., 2018; Xia et al., 2013)
		Fruit fly (*Drosophila melangaster*)	10 μM in food with or without *Lactobacillus rhamnosus* GG	*L. rhamnosus* GG prevented chlorpyrifos toxicity; abutbiotic-treated and GF flies live longer than CV flies; gut-derived *Lactobacillus*	(Daisley et al., 2018; Trinder et al., 2016)

Category	Toxicant	Model	Dose or exposure	End point and bacteria result	Source
				plantarum metabolizes chlorpyrifos to the oxon	
		Zebrafish (adult males)	30, 100 and 300 μg/L for 21 days	Altered 25 microbial genera and increased malondialdehyde and decreased glutathione in the gut	(Wang, X. et al., 2019)
	Diazinon	Mouse (8-week-old males and females)	4 mg/L in drinking water for 13 weeks	Altered expression of 677 microbial genes; disrupted quorum sensing, and enriched motility, sporulation, and stress response genes; sex-specific changes in altered bacteria	(Gao et al., 2017a; Gao et al., 2017b)
	Fenitrothion	Mosquito (*Anopheles albimanus*)	Captured mosquitos were exposed to bottles containing 50 μg fenitothion and categorized as susceptible or resistant	Resistant mosquitos had a lower bacterial diversity but an enrichment for OP-degrading bacteria and enzymes	(Dada et al., 2018)
	Malathion	Mouse (8-week-old males)	2 mg/L in drinking water (~0.6 mg/kg/day) for 13 weeks	Enrichment of genes encoding virulence, mobility, and cell wall; altered quorum sensing	(Gao et al., 2018a)
	Monocrotophos and other OPs	Mouse (8-week-old females)	28 μg/kg/day in drinking water for 30 days	Mice given fecal microbiota of monocrotophos-exposed mice had significant blood glucose intolerance	(Velmurugan et al., 2017)
Pesticide - Pyrethrin	Permethrin	Rat (90-day-old males and females)	34 mg/ 4 mL/kg per day from 6 to 21 days of age	Decreased *Provatella* family, increased *Bacteroides-Prevotella-Porphyromonas spp.* and *Bifidobacterium spp.*	(Nasuti et al., 2016)
		Mouse (adult males)	200 mg/kg permethrin and 2 mg/kg pyridostigmine bromide for 3 days in 2 week	Butyrate exposure before treatment improves proinflammatory phenotype mediated by TLR4	(Seth et al., 2018)
Pesticide - rotenoids	Rotenone	Rat (8-week-old) Mouse	2.75 mg/kg 5 days a week for 4 weeks	Increased *Bifidobacterium spp.* in colon; changes in microbiota were consistent with PD patients	(Johnson et al., 2018)
		Mouse	15–17 week old males (after training and restrain stress): 10 mg/kg/day for 6 weeks 7-week-old males: 10 mg/kg/day for 4 weeks 8–9 week-old males: 30 mg/kg/day for 4 weeks	Increased relative abundance of fecal Akkermansia Decreased *Bifidobacterium spp.* Gastrointestinal dysfunction and microbiome dysbiosis occurred before motor dysfunction; increased *Lactobacillus spp.* and decreased *Desulfovibrio spp.* associated with gastrointestinal dysfunction and motor dysfunction	(Dodiya et al., 2018; Perez-Pardo et al., 2018; Yang et al., 2017)
Pesticide-Herbicides	Atrazine	Zebrafish (4 months)	0.42 ± 0.02 μg/L for 7 days	Altered gut microbiota composition and function, but did not differ overall from control; decreased body weight and gonadosomatic index of females; induced intestinal inflammation in males	(Chen, L. et al., 2018b)
		Tree frog tadpoles and adults	178.2 ± 7.8 μg/L for 6 days	No effect on gut bacteria of tadpoles or adults	(Knutie et al., 2018)

Category	Toxicant	Model	Dose or exposure	End point and bacteria result	Source
		(*Osteopilus spetentionalis*)			
	Glyphosate	Bacteria (*in vitro* isolated from poultry)	5.0, 2.40, 1.20, 0.60, 0.30, 0.15 and 0.075 mg/ml	Pathogenic bacteria are resistant to glyphosate whereas beneficial bacteria are susceptible	(Shehata et al., 2013)
		Enterococcus spp. (in vitro from cattle and horses)	Serial dilutions from 0.001 to 10 mg/mL	All tested *Enterococcus spp.* inhibit *Clostridium botulinum*; higher concentrations of glyphosate inhibited *E. faecalis* growth but not *C. botulinum*	(Kruger et al., 2013)
		Rat	1.75 mg/kg bw/day from gestational day 6 to postnatal day 125 0.1 ppb, 400 ppm and 5000 ppm in drinking water in adults for 673 days 2.5 mg/kg/day in adults for 2 weeks	Increased *Prevotella spp.* and decreased *Lactobacillus spp.* Increased Bacteroidetes family S24–7 and a decreased Lactobacillaceae across all doses No observable short term effects; aromatic amino acids alleviate the antimicrobial effect of glyphosate	(Lozano et al., 2018; Mao et al., 2018; Nielsen et al., 2018)
		Cultural bacteria from green turtles (*Chelonia mydas*)	0.00022, 0.00044, 0.056,0.1125, 1.8, and 3.6 g/L of glyphosate from Rodeo® for 24 hours	Reduced growth and decreased survival at ceoncentrations greater than 0.00022	(Kittle et al., 2018)
		Mouse (4-week-old males)	250 or 500 mg/kg/day for 1 day, 6 weeks, or 12 weeks	Increase of anxiety and depression-like behaviors associated with decreased Firmicutes, Bacteroidetes *Corynebacterium spp.* and *Lactobacillus spp.*	(Aitbali et al., 2018)
		Honey bee (*Apis mellifera*; larva and adults)	Larva: 0.8, 4, and 20 mg/L Adults: 5 and 10 mg/L	development rate, but higher doses decreased survival; decrease in beta diversity of 20 mg/L group; increased *Acidobacteria* and *Gemmatimonadaceae* Adult: sensitivity was dependent on microbiome containing an insensitive 5-enolpyruvylshikimate-3-phosphate synthase gene; increased for opportunistic pathogen *Serratia marcescens*	(Dai et al., 2018; Motta et al., 2018)
Pesticide - Fungicide	Copper sulfate	Piglets (28-days-old)	Up to 175 mg/kg food for 2 weeks	May increase villi and crypt depth in duodenum; decreased *Enterobacteriaceae* and *Streptococci spp.*	(Hojberg et al., 2005) (Di Giancamillo et al., 2018)
Pesticide - Mixture	Boscalid, captan, chlorpyrifos, thiofanate, thiacloprid, and ziram	Mouse (16-week-old males and females)	Ziram <0.01 mg/kg food, chlorpyrifos 47 μg/kg food, thiacloprid 56 μg/kg food, boscalid 240 μg/kg food, thiofanate 205 μg/kg food, captan 165 μg/kg food for 52 weeks	In females, increased microbial associated metabolites 3-indoxyl sulphate and phenyl derivatives phenylacetylglycine and p-cresol glucuronide	(Lukowicz et al., 2018)
	Coumaphos, tau-fluvalinate, and chlorothalonil	Honey bee (Apis mellifera)	Colonies treated with tau-fluvalinate and coumaphos given strips with ~10% of the active ingredient; Colonies treated with chlorothalonil at 10	Pesiticde-dependent changes in microbiome and fungal communities; chlorothalonil increased genes for oxidative phosphorylation and decreased sugar and peptidase metabolism	(Kakumanu et al., 2016)

Category	Toxicant	Model	Dose or exposure	End point and bacteria result	Source
			µg/L in 30% sucrose; all treatments for 6 weeks		
	Lambda-cyhalothrin, deltamethrin, chlorpyrifos ethyl, spinosad and lufenuron	Bacteria from insecticide-resistant fall armyworm (*Spodoptera fruqiperda*)	*In vitro* culturing with insecticide doses of 10, 20, 40, 80, and 160 ug/mL	16 microbial strains were isolated and shown to be resistant against at least 1 insecticide	(Almeida et al., 2017)
Plant and Animal Toxins	Bamboo (cyanide)	Giant panda (*Ailuropoda melanoleuca*) and red panda (*Ailurus fulgens*)	N/A	Metagenome enriched with cyanide degrading enzymes; high abundance of *Pseudomonas*	(Zhu, L. et al., 2018)
	Domoic acid	Mollusks	N/A	Blue mussels (*Mytilus edulis*) and soft-shell clams (*Mya arenaria*) carry bacteria that can degrade domoic acid	(Stewart et al., 1998)
	Nicotine	Mouse (8-week-old males and females)	60 mg/L for 13 weeks in drinking water	Microbiome of male mice enriched for oxidative stress response, DNA repair genes, and acetate synthesis	(Chi et al., 2017c)
SCFA	propionic acid (PPA)	Human (*in vitro*; lymphoblasoid cell lines from male children with autism)	0.1, 0.5 and 1 mM	Mitochondrial function increased with PPA; however high PPA and long exposure duration increased proton leaking	(Frye et al., 2016)
Solvents	Ethanol	Mouse (6–8-week-old females)	5% for 10 days and 5 g/kg via oral gavage 9 hours prior to euthanizing	Neuroinflammation and increased SI cytokines were abbrogated in antibiotic-treated mice	(Lowe et al., 2018)
		Mouse (8–10-week-old males)	5% for 6 weeks and/or *Lactobacillus rhamnosus* GG 1×10^9 cfu daily	Increased Alcaligenes sp. and Corynebacterium sp.; *Lactobacillus rhamnosus* GG prevented hepatic injury	(Bull-Otterson et al., 2013)
		Human (adults)	Group mean 177–188 g/day	*Dorea spp.* and *Blautia spp.* were increased in alcohol dependent subjects and correlated with intestinal permeability	(Leclercq et al., 2014)
		Mouse (7-week-old females)	Up to 20% for 8 weeks	Altered genera in *Lachnospiraceae* family and decreased *Alistipes spp.*; decreased *Clostridium spp.* with saccharin co-consumption; decreased *Adlercreutzia spp.* was positively correlated with alcohol preference	(Labrecque et al., 2015; Wang et al.,2018;Xu et al., 2018)
		Rat (adults)	20% for 13 weeks (voluntary consumption)	Decreased microbiome diversity; decreased *Lactobacillus spp.*	(Kosnicki et al., 2018)
	Formaldehyde	Mouse (6 weeks old)	1 or 3 ng/mL intragastrically	Increased abundance of 13 genera and decreased 4 genera	(Guo, J. etal., 2018)
	Trichloroethylene	Mouse (gestational day 0 to postnatal day 154 or 259; females)	0.05 or 500 µg/ml	High dose, 259 day exposure, decreased *Bacteroides spp.* and *Lactobaccilus spp.* and increased *Bifidobactrium spp.* and *Enterobacteriaceae*	(Khare et al., 2019)

Table 3.

List of neurotoxicants and type of toxicity.

Toxicant	Neurotoxicity	Sources
Amiodarone	Myelinopathy	(Graham and Lantos, 1997)
	Peripheral neuropathy	(Fraser et al., 1985)
Antibiotics (unspecified)	Postpartum depression	(Murphy et al., 2018)
Arsenic	Wallerian degeneration of axons	(Klaassen, 2013)
Atrazine	Decreased serotonin	(Chen, L. et al., 2018b)
Carbamates	Inhibition of hippocampal neurogenesis, memory dysfunctions, impaired myelination	(Seth et al., 2019)
Cisplatin	Peripheral neuropathy	(Graham and Lantos, 1997)
Copper imbalance	Aceruloplasminemia, Alzheimer's disease, amyotrophic lateral sclerosis, Huntington's disease, Menkes disease, occipital horn syndrome, Parkinson's disease, prion disease, and Wilson disease	(Desai and Kaler, 2008)
Disulfiram	Peripheral neuropathy	(Graham and Lantos, 1997)
Doxorubicin	Progressive ataxia	(Graham and Lantos, 1997; Spencer and Schaumburg, 2000)
Ethanol	Worsened short-term memory, impaired neuronal signaling	(Huf et al., 2019)
	Glial dysfunction, neuroinflammation	(Gomez et al., 2018)
Formaldehyde	Neurobehavioral impairment and seizures	(Tang et al., 2011)
Gold sodium thiomalate	Decreased unmyelinated axons	(Levine et al., 1986)
Lead	ADHD	(Banerjee et al., 2007; Scassellati et al., 2012)
	Cerebral edema, lead encephalopathy, peripheral neuropathy	(Johnston and Goldstein, 1998)
Magnesium deficiency	Depression	(Winther et al., 2015)
Manganese	Parkinson's disease	(Calderon-Garciduenas et al., 2016; Dobson et al., 2004)
Methylmercury	Neuronal degeneration, ataxia, paresthesia, psychomotor retardation, developmental disabilities, and cognitive deficits	(Klaassen, 2013)
Metronidazole	Peripheral neuropathy	(Goolsby et al., 2018)
MPTP(1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine)	Parkinson's disease	(Kopin, 1987)
Nitrofurantoin	Peripheral neuropathy	(Spencer and Schaumburg, 2000)
Organochlorines	Blocks chloride channels of the GABA-A receptor, seizures, weak association with Parkinson's disease	(Costa, 2015)
Organophosphates	ADHD	(Banerjee et al., 2007; Scassellati et al., 2012)
	Over-stimulation of neurons	(Ruark et al., 2013)
	Altered serotonin signaling	Slotkin et al., 2008
Ozone	Alzheimer's disease	(Calderon-Garciduenas et al., 2016)
PM2.5	Alzheimer's disease	(Calderon-Garciduenas et al., 2016)
	Parkinson's disease	(Shin et al., 2018)

Toxicant	Neurotoxicity	Sources
Polybrominated diphenyl ethers (PBDEs)	Developmental neurotoxicity	(Dorman et al., 2018)
	Inhibited adult neurogenesis	(Li et al., 2013)
Polychlorinated biphenyls (PCBs)	ADHD	(Banerjee et al., 2007; Scassellati et al., 2012)
	Neurological deficits (differences in neuromotor development, decrements in cognition and behavioral deficits)	(Korrick and Sagiv, 2008)
	Lower cognitive functioning	(Przybyla et al., 2017)
Pyrethroids	Gulf War Illness (GWI), hippocampal volume, neural stem cell activity, and neurogenesis	(Parihar et al., 2013)
Rotenoids	Apoptosis in serotonergic and dopaminergic neurons	(Bisbal and Sanchez, 2019)
	Parkinson's disease	(Betarbet et al., 2000)
Trichloroethylene (TCE)	CNS depressant by inhibiting $GABA_A$ and glycine receptors	(Beckstead et al., 2000; Krasowski and Harrison, 2000)