Mini-Symposium

Defining Dysbiosis in Disorders of Movement and Motivation

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The gut microbiota has emerged as a critical player in shaping and modulating brain function and has been shown to influence numerous behaviors, including anxiety and depression-like behaviors, sociability, and cognition. However, the effects of the gut microbiota on specific disorders associated with thalamo-cortico-basal ganglia circuits, ranging from compulsive behavior and addiction to altered sensation and motor output, are only recently being explored. Wholesale depletion and alteration of gut microbial communities in rodent models of disorders, such as Parkinson's disease, autism, and addiction, robustly affect movement and motivated behavior. A new frontier therefore lies in identifying specific microbial alterations that affect these behaviors and understanding the underlying mechanisms of action. Comparing alterations in gut microbiota across multiple basal-ganglia associated disease states allows for identification of common mechanistic pathways that may interact with distinct environmental and genetic risk factors to produce disease-specific outcomes.

Key words: **gut microbiota; basal ganglia; compulsive behavior; motor function; Parkinson's; addiction**

Introduction

From their earliest origins, eukaryotic cells have had a symbiotic relationship with microbes, which in multicellular organisms cover nearly every surface exposed to the environment, supporting critical aspects of host metabolism and physiology (Franco-Obregón and Gilbert, 2017). In humans, an estimated ~1:1 to 10:1 ratio of microbial cells for every human cell resides within the body, with the greatest reservoir being in the digestive tract (Sender et al., 2016). This microbial community is not only large by absolute number, but by complexity as well, and consists of myriad bacterial, fungal, viral, and protozoal species. Bacteria outnumber all other members, and of these, the *Bacteroidetes* and *Firmicutes* phyla predominate (Rosenbaum et al., 2015). However, broad generalizations about their impact on the host cannot easily be made as different species, and even strains within a specific phylum can differ markedly in physiology and metabolic output (Geva-Zatorsky et al., 2017). In addition, less abundant and even rare taxa may regulate overall community structure and function and play important roles in host physiology (Jousset et al., 2017; Enaud et al., 2018).

Over the past two decades, an explosion of research has begun to detail the robust relationship between gut microbiota and the CNS. Many of the foundational studies investigating the so-called gut-brain axis were made possible by the generation of germ-free rodents, which are devoid of microbes from birth. These animals demonstrate significant alterations in host physiology and behavior, suggesting that the microbiota communicates critical signals required for normal development (Mazmanian et al., 2005; Ley et al., 2006; Diaz Heijtz et al., 2011; Neufeld et al., 2011). Additional studies have manipulated content by either administering probiotics or antibiotics, or by direct transfer of gut microbiota across model organisms. Such studies have revealed fundamental roles for the gut microbiota in regulating complex host behaviors, including social, stress-induced, and cognitive behaviors (Sudo et al., 2004; Diaz Heijtz et al., 2011; Neufeld et al., 2011; Clarke et al., 2013). More recent studies also point to a role for microbiota in sensory-motor processing, movement disorders such as Parkinson's disease (PD), motivational processes, and substance use disorders (Hsiao et al., 2013; Kiraly et al., 2016; Sampson et al., 2016). Table 1 highlights some experiments that take advantage of wholesale depletion of gut microbiota to begin to investigate the effects of gut microbiota on these disorders, which will be discussed in this review.

To date, much of the work on gut microbial modulation of brain function and output has focused on its effects on cognition,

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Table 1. Effects of microbial depletion on motor function and motivated behavior[a]

Treatment	Subject	Behavior	Description	Reference
Germ-free	C57BL/6 and Swiss-Webster mice, male	Sensorimotor	Decreased activation of intestinal sensorimotor neurons	Yano et al., 2015
Low-dose penicillin	C57BL/6 mice, male + female	Social preference	Increased preference for familiar conspecifics	Leclercq et al., 2017
Germ-free	Swiss-Webster mice, male	Social preference	Increased preference for familiar conspecifics	Desbonnet et al., 2014
High-dose antibiotic mixture	NIH Swiss mice, male	Novel object preference	Increased preference for familiar object	Desbonnet et al., 2015
Germ-free	Swiss-Webster mice, male	Novel object preference	Increased preference for familiar object	Gareau et al., 2011
High-dose antibiotic mixture	C57BL/6 mice, male	Novel object preference	Increased preference for familiar object	Fröhlich et al., 2016
Germ-free	ASO mice (Parkinson's model), male	Motor behavior	Less robust deficits in time to traverse a beam, descend a pole, and remove an adhesive from the nasal bridge	Sampson et al., 2016
Germ-free	C57BL/6 mice, male	Food consumption	Decreased caloric consumption	Rabot et al., 2010
High-dose antibiotic mixture	C57BL/6 mice, male	Drug-seeking behavior	Increased conditioned place preference	Kiraly et al., 2016

[a]Effects of germ-free status (relative to conventionally colonized mice) or treatment with antibiotics (relative to subjects not treated with antibiotics) on motor function, novelty-seeking behavior, or addiction.

stress, and social behavior, with a large focus on the cortex, hippocampus, hypothalamus, and amygdala (Sudo et al., 2004; Diaz Heijtz et al., 2011; Neufeld et al., 2011; Clarke et al., 2013; Hoban et al., 2018). This review focuses on the basal ganglia, as they play an important role in sensory motor processing and the regulation of habitual movement, which contributes to core features of many neurobehavioral disorders (Figee et al., 2016). We will highlight research that contributes to our understanding of how the gut microbiota affects body movement and compulsive-like behaviors. First, we discuss the role of gut microbiota in regulating sensorimotor circuits and behaviors that depend on these circuits. Next, we review work demonstrating a link between gut microbiota and motor dysfunction in PD. We then highlight work that draws a link between gut microbiota and compulsive behaviors, ranging from tics in autism to complex behaviors in obesity and substance addiction. Finally, we explore common themes that may indicate shared underlying mechanisms in the gut-brain connection that generate dysfunction in basal ganglia circuits.

The gut microbiota and sensorimotor circuits

The contributions of gut microbiota to sensorimotor functioning in the gut and the brain are beginning to be characterized. For instance, germ-free mice display decreased gastrointestinal sensorimotor activity, as measured by lowered overall levels of gastrointestinal motility (Yano et al., 2015). Notably, treatment of mice with the probiotic *Bacteroides fragilis* or colonization of mice with a consortium of spore-forming bacteria, was sufficient to correct gastrointestinal function, in a process mediated by microbially induced production of serotonin (Yano et al., 2015). Direct proof that microbiota affect sensory processing in the brain also comes from studies with germ-free mice, which show deficits in sensorimotor gating of the startle reflex, suggesting an inability to filter out extraneous sensory cues (Hsiao et al., 2013). Alterations in gut microbiota in individuals with neuropsychiatric conditions, such as autism and schizophrenia, may therefore contribute to sensorimotor gating deficits observed in these disorders (Hsiao et al., 2013; Kohl et al., 2013; Dinan et al., 2014). As sensorimotor gating is processed within the cortico-basal ganglia circuit, identification of mechanisms of microbial communication to this brain region that affect other aspects of basal ganglia functioning, such as motor function and compulsive behavior, will likely yield clues to how gut microbiota affect this form of sensory processing.

Gut microbiota and motor function

Work on PD has revealed a link between gut microbiota and motor function. While early studies suggested that the gut microbiota influences motor behavior, as germ-free mice exhibited increased locomotion in the open field test (Diaz Heijtz et al., 2011), it was unclear whether such a change depended on direct actions of the microbiota on motor circuits. However, a mouse model for PD revealed direct contributions of gut microbiota to disease onset and progression in behavioral and histological markers for the disorder. PD is a progressive, neurodegenerative disorder characterized by a loss of dopaminergic neurons in the midbrain, specifically within the substantial nigra pars compacta and its projections to the striatum, which impairs the initiation of movements (Hadj-Bouziane et al., 2012). Aggregation of α-synuclein has been identified as a central component of PD pathology. PD is generally considered a neuroinflammatory disease in which cytokines generated in the brain, and peripheral immune cells migrating into the brain, promote α-synuclein misfolding. However, recent work suggests an additional vagal route for inflammatory agents to promote neuroinflammation (Kannarkat et al., 2013). Injection of aggregates of α-synuclein into the intestinal wall of healthy rodents promotes prion-like formation of α-synuclein inclusion bodies along the vagus nerve and within afferent brainstem loci, thereby providing a potential pathway to the substantia nigra and dorsal striatum (Holmqvist et al., 2014; Uemura et al., 2018). In support of this, two retrospective studies found that complete vagotomy, but not partial vagotomy, which does not completely denervate vagal connections to the gut, leads to reduced risk of future diagnosis of PD (Svensson et al., 2015; Liu et al., 2017). While the function of α-synuclein remains unclear, it is of note that it is present within the enteroendocrine cells within the gastrointestinal tract (Chandra et al., 2017), and it has been suggested to assist with vesicle trafficking in neurons (Diao et al., 2013). Signals from the gut microbiota may locally induce α-synuclein pathology or increase susceptibility to other genetic or environmental risk factors (e.g., pesticides) that promote pathological α-synuclein misfolding (Brown et al., 2006).

Work by Sampson et al. (2016) points to a critical role of gut microbes in PD pathology. Thy1-α-synuclein mice ("Line 61"), which overexpress wild-type human α-synuclein, also known as α-synuclein overexpressing (ASO) mice, were protected from developing α-synuclein pathology and motor symptoms when bred under germ-free conditions. Colonization with fecal microbes from control mice and healthy human subjects both produced impaired motor function in germ-free ASO mice. However, colonizing mice with fecal microbes derived from PD patients worsened motor outcomes. This suggests that, while gut microbiota facilitates disease pathology, at least in genetically susceptible individuals, the specific microbes found in persons with PD may exacerbate disease outcomes.

Fecal microbiota collected from persons with PD, and subsequently colonized into germ-free mice, exhibited increased abundance of the Gram-negative *Proteobacteria* phylum and reduced

levels of spore-forming *Lachnospiricae* family and *Ruminococcus* genus of the *Firmicutes* phylum (Sampson et al., 2016). Similar changes to the microbiota are observed in other studies of PD patients, which are reviewed by Tremlett et al. (2017) and Sun and Shen (2018). However, no two studies report identical changes in microbiota. Some studies note increases in specific *Clostridial* species or species within the *Firmicutes* phylum (Bedarf et al., 2017; Hill-Burns et al., 2017; Heintz-Buschart et al., 2018; Qian et al., 2018), whereas others report decreases in clusters of *Clostridial* species (Hasegawa et al., 2015; Scheperjans et al., 2015; Hill-Burns et al., 2017; Li et al., 2017). *Clostridia* is a class of the *Firmicutes* phylum that contains a large number of spore-forming species that promotes serotonin production in the body (Yano et al., 2015), which may drive systemic inflammation (Patrick and Ames, 2015). However, some studies report an increase in *Lactobacillus* in PD patients (Minato et al., 2017; Petrov et al., 2017), a genus of the *Firmicutes* phylum that contains species commonly used to reduce inflammation in a number of autoimmune disease models (Plaza-Díaz et al., 2017). Potentially confounding effects across study cohorts, such as differences in drug treatment and dietary habits, may drive some of these discrepancies. However, they may also reflect specific changes within the genus level that may go undetected by the bacterial sequencing methods (e.g., 16S rRNA sequencing) used in these studies, and large-scale metagenomic analysis may provide a clearer indication of dysbiosis in PD (Poretsky et al., 2014).

Gut microbiota might contribute to several factors that promote α-synuclein misfolding in the basal ganglia, including direct vagal transmission of the misfolded protein. In the work of Sampson et al. (2016), neuroinflammation in specific-pathogen-free ASO mice was observed in the frontal cortex and striatum, but not in the cerebellum. Gut microbiota might stimulate vagal efferents to produce this effect, given that vagal nerve stimulation in rats has its most robust biophysical effects across a limited number of midbrain and forebrain areas, including the basal ganglia (Surowka et al., 2015). Additionally, it might be that toxins produced by the microbiota have differential access to different brain regions depending on the permeability of the blood–brain barrier (Yang and Chiu, 2017). Regions of the basal ganglia are situated near regions of the blood–brain barrier that are particularly leaky in PD patients (Gray and Woulfe, 2015). Regardless of the means of transmission, gut microbiota play a critical role in driving pathology in this rodent model of PD and may play an influential role in the etiology of this disease in humans as well.

Gut microbiota and repetitive behaviors

Just as components of gut microbiota may impair normal initiation of motor function, they might also affect the basal ganglia's ability to prevent behaviors, allowing the development of tics and other repetitive behaviors (Bronfeld and Bar-Gad, 2013). Fields et al. (2018b) showed that increased intestinal load of lipopolysaccharides, an inflammatory antigen derived from Gram-negative bacteria, influences repetitive behaviors. Small intestinal bacterial overgrowth is a condition wherein Gram-negative bacteria and anaerobes are overly abundant, leading to inflammatory bowel syndrome and related anxiety disorders (Posserud et al., 2007; Popa and Dumitrascu, 2015). We used oral gavage delivery of exogenous lipopolysaccharide into adult mice as a proxy for small intestinal bacterial overgrowth driven by overgrowth of Gram-negative bacteria. This treatment suppressed normal levels of repetitive circling in the open field test, without affecting general measures of locomotion, suggesting that the lipopolysaccharide treatment specifically affects compulsive behaviors without inducing a generalized sickness response (Fields et al., 2018b). In line with this, germ-free mice, which have no lipopolysaccharide, exhibit increases in compulsive-like behavior, such as repetitive digging (Nishino et al., 2013). Studying specific changes of gut microbiota in conditions that exhibit changes in locomotor and habit circuits may yield substantial clues to other bacterial components that actively modulate basal ganglia circuits.

Gut microbial changes reported in individuals with autism spectrum disorder (ASD) and in rodent models of this disorder provide further clues regarding the potential mechanisms through which gut microbiota modulate repetitive behavior. For example, several studies consistently demonstrate elevated levels of *Clostridia* in fecal samples collected from autistic subjects (Finegold et al., 2002; Song et al., 2004; Parracho et al., 2005; Martirosian et al., 2011; Li and Zhou, 2016; Finegold et al., 2017; Iovene et al., 2017; Vuong and Hsiao, 2017; Argou-Cardozo and Zeidan-Chulia, 2018). *Clostridia* produce propionic acid, a short-chain fatty acid byproduct of carbohydrate fermentation, which has been proposed to cross the blood–brain barrier and may contribute to the core social and behavioral deficits observed in autism (Shultz, 2014). In support of this, several studies show that intracerebroventricular injection of propionic acid affects autism-related social and cognitive measures, including the inability to activate goal-directed behavior switching in the water maze and T-maze (Shultz et al., 2009; MacFabe et al., 2011). Propionic acid treatment also elevated brain levels of serotonin and dopamine (Shultz et al., 2008, 2009), and induced neuroinflammation across various cortical and subcortical regions, which may contribute to the observed cognitive and behavioral deficits (Shultz et al., 2008, 2009; MacFabe et al., 2011; Shultz, 2014). However, whether the dosages of propionic acid used in these studies reflect levels found in autistic subjects remains to be determined.

If *Clostridia* and other microbiota species induce behavioral effects in autistic subjects, it will likely result from multiple activation pathways involving immune, humoral, and vagal routes. For example, *Clostridia* produce several toxic byproducts found in patients with ASD and animal models, including the uremic toxins para-cresol and 4-ethylphenylsulfate, which might also cross the blood–brain barrier and affect cortico-thalamo-basal ganglia circuits (Enomoto and Niwa, 2007; Altieri et al., 2011; Hsiao et al., 2013; Gabriele et al., 2014, 2016). Intravenous injection of 4-ethylphenylsulfate increased marble-burying behavior in juvenile mice (Hsiao et al., 2013) and para-cresol levels correlated with severity of repetitive behaviors in autistic subjects, but not with other symptoms of autism (Gabriele et al., 2014).

Levels for other gut microbial species may also be altered in patients with ASD (Li and Zhou, 2016; Vuong and Hsiao, 2017). While microbiota changes lack consistency from study to study, a unifying mechanism through which gut microbiota affect symptoms of ASD is by modifying the permeability of the gut. For example, as discussed for PD, *Prevotella* levels are inversely correlated with gut barrier permeability (Brown et al., 2011; Forsyth et al., 2011; Cakmak, 2015). In line with this, lower levels of *Prevotella* correlate with greater burdens of behavioral autistic symptoms (Kang et al., 2013; Krajmalnik-Brown et al., 2015; Strati et al., 2017; Kang et al., 2018; Qiao et al., 2018). Nevertheless, some clinical studies do not find this correlation between *Prevotella* and autism symptoms (Son et al., 2015; Strati et al., 2017). Another model for ASD, the maternal immune activation model of autism, shows an increase in *Prevotella*. However, this model also demonstrates increased gut permeability and a treat-

ment that restored the integrity of the gut barrier also normalized anxiety and repetitive behavior (Hsiao et al., 2013).

Other findings highlight the importance of investigating functional output of the gut microbiota in addition to identifying key taxa associated with ASD. For example, some studies report an increase in *Sutterella*, a member of the *Proteobacteria* phylum that may contribute to gut barrier dysfunction and systemic endotoxemia in autistic subjects (Williams et al., 2012; Wang et al., 2013); however, these findings are not reported in other studies (Strati et al., 2017; Qiao et al., 2018). Elevated levels of *Lactobacillus* species are also reported for children with ASD (Kang et al., 2013; Pulikkan et al., 2018); however, one open label clinical study successfully used *Lactobacillus* species to treat gastrointestinal and behavioral symptoms (Shaaban et al., 2017). These seemingly contradictory studies may be explained by separate bacterial strains within the same species having unique physiological and behavioral effects (Merkx-Jacques et al., 2013; Proença et al., 2017). Thus, it is important to screen for overall functional output of microbiota rather than simply noting compositional differences. This may also help researchers identify which microbial changes contribute to behavioral symptoms or may be endogenous compensatory mechanisms.

Gut microbiota and compulsive behaviors

Compulsive behaviors are observed not just across a wide spectrum of neuropsychiatric disorders, but also in behaviors not traditionally associated with neuropsychiatric disorders, such as compulsive eating. Compulsive eating may contribute to the pathophysiology of obesity in a subset of individuals (Moore et al., 2018). Obese individuals exhibit significant comorbidity with obsessive-compulsive disorder (Albert et al., 2013), along with several neurobiological markers of addiction, including increased cortico-striatal connectivity, and impaired dopamine regulation of the orbitofrontal cortex and dorsal striatum (Volkow et al., 2008, 2013; Cone et al., 2013). While the gut microbiota participates in nutrient energy harvesting and plays a role in many other aspects of host metabolism (Pascale et al., 2018), it may also drive compulsive eating. Transfer of microbiota from obese mice to those raised on a standard diet conferred many of the phenotypes observed in high-fat diet fed mice. Mice that received transfer of a microbiome from high-fat diet-fed mice showed significant propensity to become obese. Although feeding behavior itself was not measured, these mice showed increases in anxiety-like behavior on the open field test and elevated plus maze and increases in compulsive-like burying behavior in the marble-burying test. (Bruce-Keller et al., 2015).

Another set of psychiatric disorders marked by compulsive behavior in humans are the substance use disorders. Recent work has found that the gut microbiota both influences and is influenced by the effects of psychostimulant drugs and may contribute to compulsive substance use. Kiraly et al. (2016) showed that antibiotic depletion of gut microbiota in adulthood leads to increased sensitivity to the behavioral effects of cocaine in mice. Antibiotic treatment increased the development of locomotor sensitization and conditioned place preference at a dose that did not produce behavioral effects in control animals. Antibiotic treatment increased striatal expression of BDNF, a neuropeptide with wide-ranging effects on brain physiology, regardless of cocaine exposure. The increase in BDNF may serve as a trigger for downstream neurochemical effects, as both cocaine and antibiotic treatments were required to elicit changes in glutamate and dopamine receptor expression. These observations demonstrate that the gut microbiota acutely influences function and output of systems that encode motivational salience and mediate decision-making (Kiraly et al., 2016).

Putting the pieces together

The studies discussed in this review highlight similarities and differences in gut microbiota composition both within and across various basal ganglia-associated disease states, providing as many clues as questions regarding the potential effects of gut microbes on basal ganglia circuits. Changes in gut microbiota could either serve as significant or moderating factors in the etiology of these diseases, or they could simply be interesting epiphenomena. Accumulating evidence points to the former, with wholesale depletion and modification of gut microbiota either ameliorating or worsening disease state in animal models of PD (Sampson et al., 2016), obesity (Bruce-Keller et al., 2015), and cocaine addiction (Kiraly et al., 2016). Alternatively, even if the changes to the microbiota that occur during disease processes are merely a bystander effect, the continued study of these changes may provide benefit as early indicators of disease diagnosis or prognosis.

Microbiota are also required for the normal development of basal ganglia circuits, as evidenced by reduced expression of synapse-related gene expression within the striatum of germ-free mice (Diaz Heijtz et al., 2011). Microbiota actively maintain normal basal ganglia physiology in adult animals, with antibiotic depletion of gut microbiota increasing BDNF expression in the ventral striatum in conventionally colonized mice (Kiraly et al., 2016), potentially with wide-ranging effects (Song et al., 2017). While such studies suggest that microbiota may affect basal ganglia function and behavioral output, the mechanisms underlying these effects remain unknown.

To address this question, it is first important to acknowledge the extensive functional redundancy within gut microbiota (Allison and Martiny, 2008). For example, the Human Microbiome Project revealed that it is possible for two healthy human individuals to share minimal to no overlap in microbial species composition (Gilbert et al., 2018). This functional redundancy may explain some of the contradictory findings of changes in gut microbiota within the diseases discussed here. For example, original studies on gut microbial changes within obese subjects reported increases in the *Firmicutes*-to- *Bacteroidetes* ratio in both obese rodents and humans (Ley et al., 2005; Turnbaugh et al., 2006). However, subsequent work either found no changes in this ratio (Duncan et al., 2008; Million et al., 2013; Rosenbaum et al., 2015) or an inverse of this ratio in obese subjects (Schwiertz et al., 2010; Ignacio et al., 2016), along with more fine-grained increases and decreases of species within both the *Firmicutes* and *Bacteroidetes* phyla within obese subjects (Bruce-Keller et al., 2015; Jung et al., 2018). Nevertheless, later work also confirmed the finding of an increased *Firmicutes*-to-*Bacteroidetes* ratio in some obese subjects, suggesting that this compositional change may serve as a significant factor in a subset of the disease (Koliada et al., 2017). These findings were accompanied with the observation of other common changes, such as increases in the *Actinobacteria* phylum, that may increase energy harvesting and compulsive eating (Koliada et al., 2017).

Consideration of common effects of compositional changes within the gut microbiota across various basal-ganglia associated disorders may shed light on the core functional consequences that may drive basal ganglia pathology. One potential core mechanism may be increases in gut permeability, which may be mediated by several dysbiotic changes in gut microbiota. As discussed, *Prevotella* may serve as a protective factor against barrier dysfunction, and is lower in abundance in subjects with PD and autism

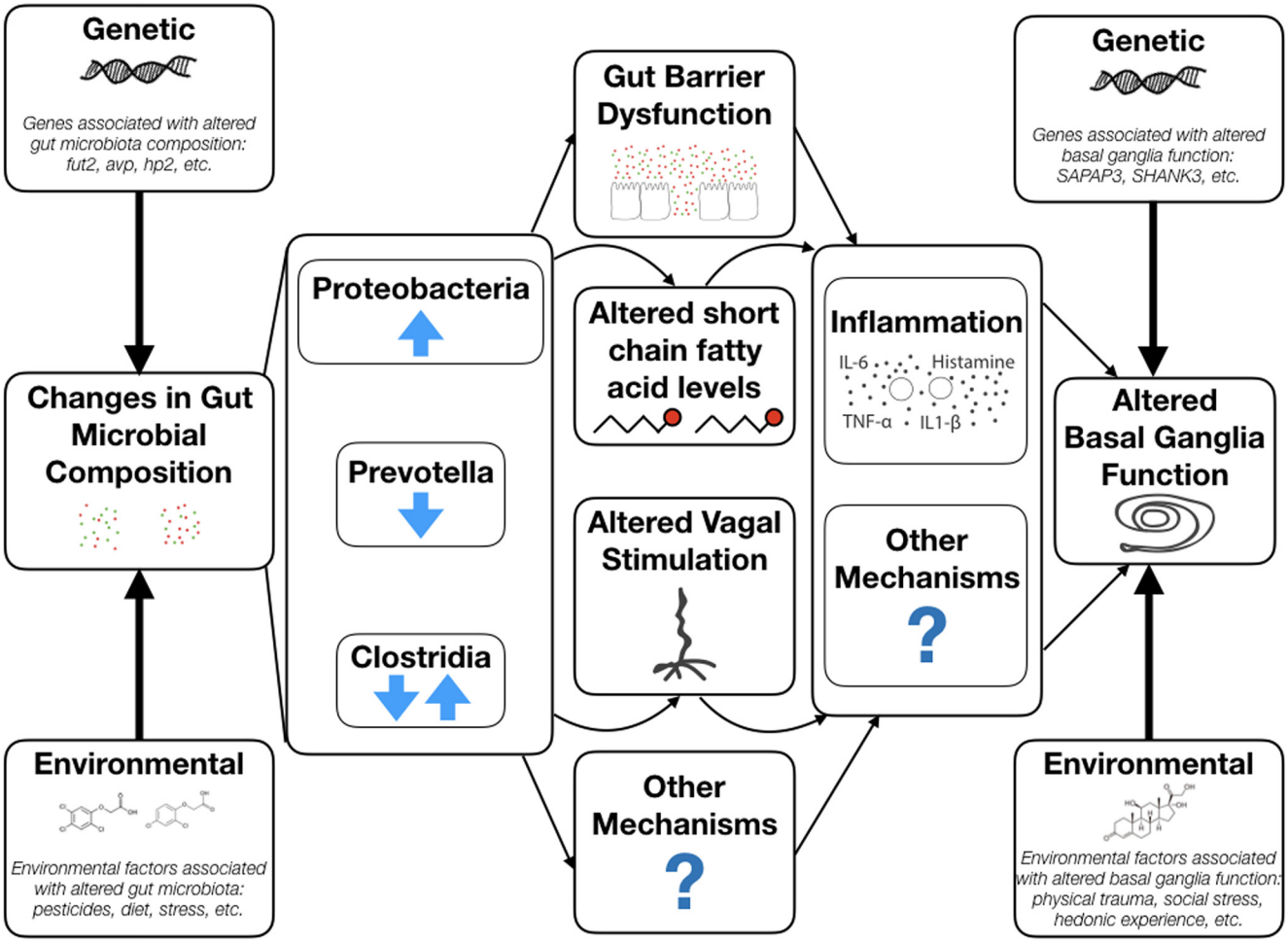

Figure 1. Gut microbial alterations occur within the context of genetic and environmental factors that shape basal ganglia-associated disease susceptibility. These host factors affect both gut microbial composition and basal ganglia function. Common microbial alterations associated with increased disease risk include increases in *Proteobacteria*, decreases in *Prevotella*, and alterations in *Clostridia*, which are all associated with increased gut barrier dysfunction. Other risk factors, such as altered short-chain fatty acid levels, increased vagal activation, and other mechanisms (e.g., the release of other bacterial metabolites) may also result from gut microbial alteration. Increased systemic inflammation and neuro-inflammation are common endpoints of all of these alterations, but other gut-to-brain mechanisms also contribute to basal ganglia disease etiology. Ultimately, gut-derived factors that alter basal ganglia function interact with other preexisting genetic and environmental susceptibility factors to shape specific disease outcomes.

(Kang et al., 2013; Hasegawa et al., 2015; Keshavarzian et al., 2015; Krajmalnik-Brown et al., 2015; Scheperjans et al., 2015; Unger et al., 2016; Bedarf et al., 2017; Strati et al., 2017; Kang et al., 2018; Qiao et al., 2018), but animal models of the disorder also exhibit increases in *Prevotella* along with increases in gut permeability (Hsiao et al., 2013). Overgrowth of Proteobacteria, which is observed in PD (Forsyth et al., 2011; Keshavarzian et al., 2015; Scheperjans et al., 2015; Unger et al., 2016; Li et al., 2017; Qian et al., 2018) and autism (Williams et al., 2012; Wang et al., 2013), along with obesity (Cani et al., 2007) and cocaine addiction (Volpe et al., 2014), can also stimulate increases in intestinal permeability (Jakobsson et al., 2015), primarily mediated through activation of innate immune receptor TLR4 by its cell surface antigen lipopolysaccharide (Guo et al., 2015). However, here too, noting increases in *Proteobacteria* are insufficient to infer functional consequences, as even different strains of *Escherichia coli*, a species in the *Proteobacteria* phylum, carry lipopolysaccharide molecules with differing levels of immunogenicity, with some serving as TLR4 agonists and others as TLR4 antagonists (Coats et al., 2005). Current high-throughput gut microbiota sequencing efforts, which identify bacteria by a portion of its 16S rRNA signature, cannot distinguish between strains, and some sequence tags fail to discriminate beyond the genus or family level (Fukuda et al., 2016). Assays built to distinguish species and strain-level differences in composition within taxa will allow for investigation of the neurobiological effects of specific microbes with either gnotobiotic models or targeted elimination (e.g., narrow-spectrum bacteriophage-derived treatments such as lysin therapies that eradicate specific bacterial species) (Pastagia et al., 2013). In addition, metabolic profiling of strains exhibiting the most robust compositional changes may provide clues regarding the overarching functional consequences of observed compositional changes.

A specific etiologic trigger, such as gut barrier dysfunction, which may be precipitated by several different changes in bacterial composition, likely interacts with several environmental and genetic risk factors to precipitate specific disease outcomes. This model is highlighted in Figure 1. Increases in gut barrier dysfunction may alter other gut microbial communication pathways to the brain, which may include modifying systemic short-chain fatty acid levels and afferent vagal activity. For example, both rare mutations and ingestion of environmental toxins have been suggested to contribute to disease onset in PD patients, perhaps leading to a greater rate of

α-synuclein misfolding along the vagus nerve (Smith and Parr-Brownlie, 2018; Zeng et al., 2018).

Sex differences in various host systems, such as the immune system (Klein and Flanagan, 2016), may combine with dysbiotic changes in gut microbiota to exacerbate disease outcomes in one or the other sex. For example, bacterial antigens may activate differing types of inflammation in males and females (e.g., generate a more pro-allergic immune profile in males) (Kelly and Gangur, 2009), which promote differing types of neuroinflammation with potentially different behavioral effects. On the other hand, Fields et al. (2018a) revealed that a common microbial antigen elicited similar behavioral but differential immune responses in males and females (Fields et al., 2018a). Only a few studies have directly investigated how gut microbiota and host sex factors interact. For example, one landmark study by Markle et al. (2013) identified robust sex differences in gut microbiota in adult mice and revealed that gut microbiota from males when transferred to females may elevate testosterone levels in females (Markle et al., 2013). The recent National Institutes of Health' mandate to include both female and male subjects in biomedical research should undoubtedly be applied to the study of gut microbiota, which is likely to reveal many more sex-specific effects of gut microbiota on the host.

Gut barrier dysfunction is not the only gut microbiota-associated factor that has context-specific effects. Short chain fatty acids have been associated with both proinflammatory and anti-inflammatory effects, based on host context (Kuo et al., 2014; Zhang et al., 2016). Furthermore, short chain fatty acid treatment was shown to promote PD motor defects (Sampson et al., 2016) but to protect against sensitization to cocaine (Kiraly et al., 2016). These are not likely the only gut microbiota-associated factors that affect host biology differently based on context. Furthermore, these gut microbial effects are likely to both converge and cancel each other out, so identifying dominant factors within each disease state will be key to identifying prominent mechanisms of action.

From vagal stimulation to systemic breach of gut-derived toxins and from stimulation of systemic inflammation to systemic release of bacterial metabolic byproducts, such as short chain fatty acids, these mechanisms of action can be driven by multiple compositional profiles and can have differential effects based on host biology. Future studies will need to further identify not only compositional differences in gut microbiota associated with health and disease, but also the context-specific functional effects of these microbial alterations. This will serve as a critical step toward developing therapies for basal ganglia-associated disorders targeted at gut microbial manipulation.

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