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University College Cork, Ireland
Coláiste na hOllscoile Corcaigh

The Microbiota-Gut-Brain Axis

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II. Abbreviations

5-HT – 5-hydroxytryptamine or serotonin

5-$HT1_A$ - serotonin 1A receptor

α-MSH - α-Melanocyte-stimulating hormone

A. muciniphila - Akkermansia muciniphila

Aβ - Amyloid β

ACTH Adrenocorticotropic hormone

AD – Alzheimer's disease

ADHD - Attention deficit hyperactivity disorder

AH - After-hyperpolarization

ALS - Amyotrophic Lateral Sclerosis

AMPA - α-amino-3-hydroxy-5-methylisoxazole-4-propionate

ANS – Autonomic nervous system

APP - Amyloid precursor protein

ASD - Autism spectrum disorder

ASF - Altered schaedler flora

ASO - α- synuclein overexpressing

ATP - Adenosine triphosphate

B. acidophilus– Bifidobacterium acidophilus

B. adolescentis – Bifidobacterium adolescentis

B. animalis – Bifidobacterium animalis

B. bifidum – Bifidobacterium bifidum

B. breve – Bifidobacterium breve

B. catenulaturm– Bifidobacterium catenulaturm

B. dentium– Bifidobacterium dentium

B. fragilis – Bifidobacterium fragilis

B. infantis– Bifidobacterium infantis

B. lactis – Bifidobacterium lactis

B. longum – Bifidobacterium longum

B. subtilis – Bifidobacterium subtilis

B. fragilis - Bacteroides (B.) fragilis

B-GOS® - Bimuno-galactooligosaccharide

BBB – Blood-brain barrier

BCAA – Branched-chain amino acid

BCAAem – BCAA mixture

BCE – Before current era

BDNF – Brain-derived neurotrophic factor

BMI – Body mass index

BPA - Bisphenol A

BSH - Bile salt hydrolase

C. rodentium – Citrobacter rodentium

C. butyricum - Clostridium butyricum

C. perfringens - Clostridium perfringens

C. difficile - Clostridium difficile

C-section – cesarean section

CA - *Cornu ammonis*

CCK - Cholecystokinin

CDI - *Clostridium difficile* infection

ClpB - Caseinolytic protease B

CNS – Central nervous system

CRD – Colorectal distension

CRF - Corticotropin-releasing factor

CSF - Cerebrospinal fluid

CVD - Cardiovascular disease

DNA - Deoxyribonucleic acid

E - Embryonic day

E. coli - Escherichia coli

E. rectale - Escherichia rectale

eAAs – Essential amino acids

EC - Enterochromaffin cell

EECs - Enteroendocrine cells

ENS – Enteric nervous system

EPM - Elevated plus maze

EU - European union

FBA - Flux Balance Analysis

FFAR – Free fatty acid receptor

FGF - Fibroblast growth factor

FGID - Functional gastrointestinal disorder

fMRI – Functional magnetic resonance imaging

FMT - Fecal microbiota transplant

FODMAP - Fermentable oligosaccharides, disaccharides, monosaccharides and polyols

FOS – Fructooligosaccharide

FST - Forced-swim test

FXR - Farnesoid X receptor

GABA - γ-aminobutyric acid

GENREs - Generation and refinement of genome-scale metabolic reconstructions

GCN2 - General control nonderepressible 2

GF – Germ-free

GI – Gastrointestinal

GLP-1 - Glucagon-like peptide-1

GOS – Galactooligosaccharide

GPCR – G-protein coupled receptor

GRIN - Glutamate [NMDA] receptor subunit

GWAS - Genome wide association studies

HDAC – Histone deacetylase

HFD – High-fat diet

HIV – Human immunodeficiency virus

HPA - Hypothalamic-pituitary-adrenal

HSV-1- Herpes simplex virus 1

IBD - Inflammatory bowel disease

IBS - Irritable bowel syndrome

IDO - Indoleamine-2,3-dioxygenase

IFN – Interferon

IL – Interleukin

L. acidophilus – Lactobacillus acidophilus

L. brevis– Lactobacillus brevis

L. bulgaricus – Lactobacillus bulgaricus

L. casei – Lactobacillus casei

L. curvatus – Lactobacillus curvatus

L. delbrueckii – Lactobacillus delbrueckii

L. farciminis– Lactobacillus farciminis

L. fermentum– Lactobacillus fermentum

L. helveticus – Lactobacillus helveticus

L. johnsonii– Lactobacillus johnsonii

L. paracasei – Lactobacillus paracasei

L. plantarum – Lactobacillus plantarum

L. reuteri – Lactobacillus reuteri

L. rhamnosus – Lactobacillus rhamnosus

L. salivarius– Lactobacillus salivarius

LPS – Lipopolysaccharides

LTP – Long-term potentiation

MDD - Major depressive disorder

MDS - Multidimensional scaling

mGlu - Metabotropic glutamate

MMSE - Mini mental state exam

MRI - Magnetic resonance imaging

mRNA - Messenger ribonucleic acid

MRS - Magnetic resonance spectroscopy

MS - Multiple sclerosis

mTOR – Mammalian target of rapamycin

MWM - Morris water maze

NF_KB - Nuclear factor kappa-light-chain-enhancer of activated B cells

NMDA - N-methyl-D-aspartate

NMDAR - NMDA receptor

NOD1/2 - Nucleotide-binding oligomerization domain-containing protein ½

NOR – Novel object recognition

NPY - Neuropeptide Y

NSAIDs – Non-steroidal anti-inflammatory drugs

NTS - Nucleus tractus solitarii (the nucleus of the solitary tract)

OCD - Obsessive-compulsive disorders zf

Olfr78 – Olfactory receptor 78

OFT - Open-field test

OR51E1 - Olfactory receptor 51E1 is

OSA - Obstructive sleep apnea

PCB - Polychlorinated biphenyl

PCR – Polymerase chain reaction

PCA - Principle component analysis

PCR - Polymerase chain reaction

PD - Parkinson’s disease

PFC – Prefrontal cortex

PGLN - Peptidoglycan

PGLYRP - Peptidoglycan recognition proteins

PICRUSt - Phylogenetic investigation of communities by reconstruction of unobserved states

PNS - Peripheral nervous system

PPI – Proton pump inhibitor

PRRs - Pattern recognition receptors

PS1 – Presenilin 1

PTSD - Post traumatic stress disorder

PUFA - Polyunsaturated fatty acids

PVN - Paraventricular nucleus

PYY – Peptide YY

Rag2 - Recombination activation gene 2

RNA - Ribonucleic acid

RS - Resistant starche

S. thermophilus - *Streptococcus (S.) thermophilus*

SCFA – Short-chain fatty acid

SIT - Social interaction test

SPF – Specific pathogen-free

T2DM - Type II diabetes mellitus

TBI - Traumatic brain injury

TCA - Tricyclic antidepressants

TDO - tryptophan-2,3-dioxygenase

TGF - Transforming growth factor

TGR5 - G-protein coupled bile acid receptor Gpbar1 receptor

TLR – Toll-like receptor

TNF-α/β - Tumor necrosis factor alpha/beta

TPH1 - Tryptophan hydroxylase

TRPV1 - Transient receptor potential vanilloid 1

UPDRS - Unified Parkinson's disease rating scale

VNS - Vagus nerve stimulation

VPA - Valproic acid

WGS - Whole genome shotgun sequencing

III. Abstract

The importance of the gut-brain axis in maintaining homeostasis has long been appreciated. However, the past 15 years have seen the emergence of the microbiota (the trillions of microorganisms within and on our bodies) as one of the key regulators of gut-brain function and has led to the appreciation of the importance of a distinct microbiota-gut-brain axis. This axis is gaining ever more traction in fields investigating the biological and physiological basis of psychiatric, neurodevelopmental, age-related and neurodegenerative disorders. The microbiota and the brain communicate with each other via various routes including the immune system, tryptophan metabolism, the vagus nerve and the enteric nervous system (ENS), involving microbial metabolites such as short-chain fatty acids (SCFAs), branched chain amino acids (BCAAs) and peptidoglycans. Many factors can influence microbiota composition in early life, including infection, mode of birth delivery, use of antibiotic medications, the nature of nutritional provision, environmental stressors, and host genetics. At the other extreme of life, microbial diversity diminishes alongside with aging. Stress, in particular, can significantly impact the microbiota-gut-brain axis at all stages of life. Much recent work has implicated the gut microbiota in many conditions including autism, anxiety, obesity, schizophrenia, Parkinson's disease and Alzheimer's disease. Animal models have been paramount in linking the regulation of fundamental neural processes, such as neurogenesis and myelination, to microbiome activation of microglia. Moreover, translational human studies are ongoing and will greatly enhance the field. Future studies will focus on understanding the mechanisms underlying the microbiota-gut-brain axis and attempt to elucidate microbial-based intervention and therapeutic strategies for neuropsychiatric disorders.

IV. Introduction

"All disease begins in the gut."

– Hippocrates of Kos (Hippokrátēs ho Kṓos: c. 460 – c. 370 BCE)

It was over two thousand years ago when the Greek physician Hippocrates, oft-lauded as the father of modern medicine, is purported to have made this proclamation. Although the attribution to Hippocrates has been questioned, its inherent wisdom continues to influence researchers and practitioners in medicine (and beyond) regardless of its authenticity (Dinan and Cryan, 2016).

Although the links between rural Michigan and ancient Greece are not obvious, it was there in the 1800s that an unfortunate injury to a Canadian fur-trader Alexis St. Martin created a serendipitous opportunity to advance the study of the gut and digestion in line with the sentiments of Hippocrates and the other great Greek physician-philosopher, Galen of Pergamon (Mattern, 2013). St. Martin was accidentally shot at close range and, during his treatment by the US Army surgeon William Beaumont, became one of the most famous patients in gastroenterology (Beaumont, 1833). The surgery left St. Martin with a fistula in his gut, a window into the intestine, for Beaumont to study. The doctor took careful notes throughout the recovery period and discovered the manner in which many aspects of digestion occurred via experiments where he inserted food into St. Martin's stomach, then later removing it to observe the extent of digestion. He took gastric secretion samples and sent them to chemists of the day for analysis, a very uncommon medical process for the mid-19th century. This was one of the first recorded observations of human digestion taking place in real time. Even more fascinating were Beaumont's notes of "pain and uneasiness" at corporeal sites far from the wound, linking digestion with disease, and emotionality. Moreover, when St Martin became angry or irritable, it greatly affected the rate of digestion, indicating that the subject's emotional state affected digestion i.e. there was a brain-gut axis. Notwithstanding the discomfort of his patient, Beaumont's work moved the field beyond the 2nd-century teachings of Galen (Mattern, 2013) to pioneer a new era of precise clinical data collection, observation, and recording of conclusions for future reference. Other great historical scientists, including Charles Darwin (Ayala, 2009) and Claude Bernard (Bernard, 1949 (Originally 1865)), continued the effort to formally establish and standardize the use of the scientific method in medicine. While Darwin was fastidiously investigating, collecting and cataloging biological specimens to build evidence for his famed theory of natural selection (Darwin, 1859), Bernard was practicing the scientific method at the Sorbonne and the Natural History Museum in Paris, France. Through his feeding experiments with rabbits, Bernard determined the process for the emulsification and saponification of fats by the pancreas and identified that the process of digestion took place not in the stomach but the small intestine. Further studies of glycogen stores in the liver and blood sugar levels illustrated that digestion not only breaks up complex molecules from food but also stores them for future energy requirements. Encapsulating his body of research, Bernard developed the concept of *milieu intérieur*, stating that "The stability of the internal environment is the condition for the free and independent life" (Bernard, 1878). This would later become the foundation for our understanding of corporeal homeostasis.

Bernard, as one of the earliest pioneers of animal experimentation, also paved the way for future scientific discovery. Amongst those following in this tradition was Ivan Pavlov, whose defining studies of classical conditioning were directly inspired by William Beaumont's observations of digestion. Under the tutelage of Carl Ludwig in Leipzig, Germany, Ivan Pavlov helped develop the Pavlov pouch (Pavlov, 1897), a piece of exteriorized dog intestine used to study the processes of digestion in dogs. He perfected the technique by maintaining the innervation to the exteriorized intestine section to allow more accurate measurement of digestive processes in real time over extended periods; it is believed that this is one of the first recorded uses of a chronic model of animal experimentation in modern science. These studies set the basis for our understanding of the critical role that the gut-brain axis plays in homeostatic processes in health and disease. With the advent of brain imaging technology in the 1980s, the full appreciation of the bidirectionality of this axis emerged. Studies showed that distention of the gut, resulted in activation of key pathways within the brain and that such pathways are exaggerated in disorders such as irritable bowel syndrome (IBS), a functional GI disorder with dysregulated microbiota-gut-brain axis (Farmer and Aziz, 2014; Kennedy et al., 2014; Mayer, 2000). Moreover, the gut-brain axis is seen as an important node in mammalian interoception (Craig, 2009).

Finally, in the past decades, a new player has emerged as a key regulator of the gut-brain axis, the trillions of microbes within the gut, the microbiota. Five separate lines of evidence converged to establish this. Firstly, studies in germ-free (GF) animals showed that the brain is affected in the absence of microbiota (see **Table 2**) (Clarke et al., 2013; Diaz Heijtz et al., 2011; Gareau et al., 2011; Hegstrand and Hine, 1986; Neufeld et al., 2011; Sudo et al., 2004). Secondly, animals given specific strains of bacteria had alterations in behavior (Bercik et al., 2011a; Bravo et al., 2011; Desbonnet et al., 2015; McKernan et al., 2010; Savignac et al., 2014; Verdu et al., 2008) and human studies of such strains confirmed the potential translatability of such findings (Allen et al., 2016; Pinto-Sanchez et al., 2017b; Tillisch et al., 2013). Thirdly, population-based studies of people exposed to infection, most notably in Walkerton in Canada, demonstrated alterations in gut-brain symptoms (Thabane et al., 2010). These findings were also echoed in animal studies where low-level infections altered behavior even in the absence of immune activation (Lyte et al., 1998). Fourthly, preclinical studies with antibiotic administration, either in early life (O'Mahony et al., 2014) or adulthood (Verdu et al., 2008), have shown long-lasting effects on brain, spinal cord, and the ENS. Finally, these data synergized with the long known clinical situation that hepatic encephalopathy could be broadly treated by targeting the microbiota with antibiotics in humans (see (Collins, 2016)). Once it was understood that our commensal friends in the gut could effectively communicate with our brain, a rush of studies sought to understand the intricate processes involved. The concept of the microbiota-gut-brain axis thus emerged (Cryan and O'Mahony, 2011; De Palma et al., 2014; Rhee et al., 2009) based upon the rich historical legacy of the illustrious scientific figures discussed above, amongst many others.

In this review, we aim to give the reader a comprehensive overview of how this field has pushed the frontiers of our understanding about the influence of the microbiota on our bodies and on our minds, and what still remains to be understood in order to fully realize the potential for microbiota-based medicine.

D. Microbiota: Friends with Benefits

We are living in a microbial world. Microbes have inhabited the earth for hundreds of millions of years longer than humans, and there has never been a time when our body has not received signals from microbes. The human microbiota is the collective term for the trillions of microorganisms that live in and on us (Ursell et al., 2012)Ribosomal, 16S/analysis</keyword><keyword>Sequence Analysis</keyword></keywords><dates><-year>2012</year><pub-dates><date>Aug</date></pub-dates></dates><isbn>1753-4887 (Electronic. Over the past two decades, microbiome research has accelerated at an incredible pace and is revealing the myriad of ways these microscopic inhabitants are impacting our daily lives. It is now apparent that the microbiota is a critical determinant of human health and disease and a key regulator of host physiology. In terms of numbers, the sheer scale of the microbiota is so vast. Advances in sequencing technologies coupled with microbiome bioinformatic pipeline development are making analysis of microbiota composition cheaper and more sophisticated. Indeed, initial estimates that we had ten times more microbial cells than human cells have recently been revised downwards from a 10:1 ratio to that of 1.3:1 (Sender et al., 2016). This is still an awe-inspiring figure to wrestle with. Even more so at the genetic level, more than 99% of the genes in our bodies are microbial, numbering over 10 million (D'Argenio and Salvatore, 2015; Dinan et al., 2015; Donia et al., 2014; Gill et al., 2006; Nicholson et al., 2005; Qin et al., 2010). As we have co-evolved with this microbiota, it plays a key role in programming all other bodily systems (D'Argenio and Salvatore, 2015; Walsh et al., 2014). While our inherited genome is essentially stable for the lifetime of the host, the microbiome is immensely diverse (Mosca et al., 2016; Pasolli et al., 2019), dynamic (Lloyd-Price et al., 2017), and responsive to external input, enhancing its potential as a target for therapeutic intervention (see **Section III**).

There is a distinct microbiome in almost every niche of the human body. However, the main sites of human microbial colonization are the skin, the airways, the urogenital tract, the eyes, and the gastrointestinal (GI) tract. While it is appreciated that other sites such as the oral (Kilian et al., 2016) and pulmonary microbiota (Lynch, 2016) are important, the majority of our microbial inhabitants reside in the gut. The intriguing complexity of this microbial community, alongside the fact that certain gut microbes tend to grow well in laboratory environments, has resulted in the gut microbiota being historically the most well studied of our microbial biogeographical niches. The gut hosts a diverse population of microorganisms including yeasts, archaea, parasites such as helminths, viruses, and protozoa, but the bacterial population is currently the most well characterized (Eckburg et al., 2005; Gaci et al., 2014; Lankelma et al., 2015; Scarpellini et al., 2015; Williamson et al., 2016).

Current ongoing large collaborative efforts including the Human Microbiome Project (Human Microbiome Jumpstart Reference Strains et al., 2010; Human Microbiome Project, 2012), MetaHIT (Li et al., 2014; Qin et al., 2010), American Gut Project (McDonald et al., 2018), British Gut Project (Jackson et al., 2018), as well as important gut microbiome cohort analyses (Falony et al., 2016; Zhernakova et al., 2016) have been instrumental in surveying and describing the gut microbiota at a population level. Current combined Human Microbiome Project and MetaHIT data estimate that there are at least 2776 prokaryotic species that have been isolated from human fecal matter. These have been classified into 11 different phyla with Proteobacteria, Firmicutes, Actinobacteria and Bacteroidetes comprising over 90% of the microbiome (Bilen et al., 2018; Hu-

gon et al., 2015; Li et al., 2014), while Fusobacteria and Verrucomicrobia phyla are present in low abundance (Eckburg et al., 2005).

We are only at the beginning of understanding what relative shifts in the microbiome correspond to functionally. Thus in this review, although we endeavor to report broad correlations between large obvious compositional changes in the microbiota, in many instances it is not yet possible to define a causal role for these correlational observations. This endeavor is further complicated by the fact that the fine structure of the healthy microbiota seems to be unique to individuals; intra-individual differences across time are typically much smaller than differences between individuals (Caporaso et al., 2011; Costello et al., 2009). Incredibly, recent findings have identified an elementary layer of variability in the microbiome identified as microbial genomic structural variants (the term pertaining to the existence of a few genes which are different between otherwise identical bacterial strains) that are specifically unique to the host microbiota and demonstrate a strong association with host metabolic health (Zeevi et al., 2019). As a result, throughout this review, we will state outcomes from studies on a case-by-case basis and will discuss where possible when it is known if the changes seen are causative or correlative. What does appear to be important, however, is maintenance of homeostasis for each balanced compositional signature with disruption of this homeostasis conferring disease susceptibility (Lin and Zhang, 2017), such as that found with colorectal cancer (Wirbel et al., 2019). Despite the challenges posed by such wide inter-individual variation, some have attempted to classify human gut microbiota colonies into different enterotypes (Arumugam et al., 2011). While this classification system remains somewhat controversial (Costea et al., 2018) and over-simplistic (Knights et al., 2014) three distinct enterotypes have been proposed, each of which is characterized by relatively high levels of a single microbial genus: *Bacteroides., Prevotella.* or *Ruminococcus*. (Arumugam et al., 2011; Roager et al., 2014). These enterotypes do seem to have some functional relevance with the *Bacteroides*. enterotype being associated with high fat or protein diets, and the *Prevotella*. enterotype with high-carbohydrate diets (Wu and Hui, 2011).

It is hoped that future studies in the field will capitalize on newer technologies, such as whole-genome shotgun metagenomics, which provide higher resolution and sensitivity in microbiome analysis. Currently, metagenome-wide association studies are being conducted (Wang and Jia, 2016; Wang et al., 2018b) (see **Section II.G**). If lessons are learned from Genome-Wide Association Studies (GWAS) in human genetics, such studies will not only allow more reliable estimates of the composition and diversity of our microbiome, but also provide valuable insight into the functional potential of the microbiome as we seek to understand its influence on the host and the gut-brain axis in particular (Poretsky et al., 2014; Tessler et al., 2017). Moreover, the importance of metabolomic analysis in going beyond describing what microbes are there to what they are doing has become increasingly informative (Zierer et al., 2018). The most recent combination analysis using GWAS of the microbiome and metagenomic sequencing has discovered a causal effect of the gut microbiome on metabolic traits, suggesting increased gut butyrate production associated with improved insulin response after an oral glucose-tolerance test, but errors in production or absorption of propionate causally related to enhanced risk of type II diabetes (Sanna et al., 2019). One can only hope that studies like these propagate quickly in the field given their immense potential to inform alternative therapies for human diseases.

E. Gut-Brain Axis

As previously described, the GI tract exerts an influence on brain function, and vice versa (**See also Section IV**). Much of the earlier work regarding gut-brain communication concentrated on digestive function and satiety (Berthoud, 2008a; Konturek et al., 2004; Tache et al., 1980), but recent research has taken an increasing focus on higher-order cognitive and psychological effects of gut-to-brain and brain-to-gut communication (Agusti et al., 2018; Carabotti et al., 2015; Rhee et al., 2009; Sarkar et al., 2016). Through this research, we now understand some of the pathophysiological consequences of an aberrant reciprocal gut-brain network, including exacerbated gut inflammation disorders (Bernstein, 2017; Breit et al., 2018; Mayer et al., 2015b), altered responses to acute and chronic stress (Dinan and Cryan, 2017; Foster et al., 2017; Gao et al., 2018; Maniscalco and Rinaman, 2018; Marin et al., 2017; Partrick et al., 2018; Provensi et al., In Press; Sun et al., 2018), as well as altered behavioral states (Arentsen et al., 2018; Dinan and Cryan, 2017; Foster et al., 2017; Heintz-Buschart et al., 2018; Jaglin et al., 2018; Luk et al., 2018; Maniscalco and Rinaman, 2018). As a result, the gut-brain axis presents an attractive target for the development of novel therapeutics for an ever-growing list of disorders related to mental health and cognitive function (Clapp et al., 2017; Dinan and Cryan, 2017; Jiang et al., 2017; Tognini, 2017) obesity (Torres-Fuentes et al., 2017), and GI disorders such as inflammatory bowel disease (IBD) (Bernstein, 2017; Bonaz and Bernstein, 2013) and IBS (Collins et al., 2012; Mayer, 2011). Improved targeting of the gut-brain axis, for example through application of psychobiotics (targeted microbiota interventions that support good mental health) (Allen et al., 2016; Sarkar et al., 2016; Valles-Colomer et al., 2019), is expected to pave the way for the development of novel disease therapies (Sherwin et al., 2018) (see **Section VIII**).

F. Microbiota-Gut-Brain Axis

Over recent decades, the fields of microbiology and neuroscience have become ever more entwined. Although the concept of a microbiota-gut-brain axis is relatively new, it is becoming increasingly accepted that the resident microbiota can exert considerable influence over host behavior (Cleary et al., 2017; Clemente et al., 2012; Karst, 2016; Sekirov et al., 2010; Turroni et al., 2018), which we shall illustrate in **Section X**. (Behavior and the Microbiota-Gut-Brain Axis), and **Section XI**. (Diseases and Disease Processes). Bidirectional communication along the gut-brain axis is a fundamental aspect of the synergy between microbiota and host in accessing gut-brain signaling pathways to modulate host brain and behavior (see **Section VII**. (Cryan and Dinan, 2012; Dinan and Cryan, 2017; Grenham et al., 2011; Mayer et al., 2015b; McVey Neufeld et al., 2015; Rhee et al., 2009). The studies conducted to identify and examine the microbiota-gut-brain axis have used different, yet complementary microbiota interventions, including GF rodents (see **Table 2**) (Luczynski et al., 2016a; Luk et al., 2018), antibiotic-induced depletion (see **Table 3**) (Desbonnet et al., 2015; Guida et al., 2018; Staley et al., 2017), prebiotic/probiotic supplementation (see **Tables 4 and 5**) (Burokas et al., 2017; Fukui et al., 2018; Grimaldi et al., 2018; Kao et al., 2018; Kazemi et al., 2019; Tabouy et al., 2018), GI infection (Harris et al., 2017; Zuo et al., 2018), and fecal microbiota transplantation (FMT) (see **Section V.C.**) (Cryan and Dinan, 2015b; Sherwin et al., 2016a; Singh et al., 2018a; Zhou et al., 2017), all of which will be discussed in greater detail in **Section IV**.

G. Evolution, Microbiota and the Holobiont

It is important to contextualize the recent appreciation of the microbiome on host health in an evolutionary context. Over time the microbiota has co-evolved with host organisms, becoming mutually co-dependent for survival (Bordenstein and Theis, 2015; Gaulke et al., 2018). Given that there has never been a time when mammals existed without microbes (apart from under highly restrictive laboratory conditions), there has also never been a time when the brain has been without signals from the gut, and it is important to consider the relationship between the host and its microbiota from an evolutionary perspective (Stilling et al., 2014a). The concept of the holobiont has been developed to describe the ecological unit comprising both the host species and its symbiotic microbiota (Bordenstein and Theis, 2015; Shropshire and Bordenstein, 2016; Zilber-Rosenberg and Rosenberg, 2008). This, in turn, has led to the hologenome theory of evolution, which suggests that the holobiont and its associated hologenome acts as a unit of evolutionary selection (Zilber-Rosenberg and Rosenberg, 2008). One key principle of the hologenome theory is that genetic variation in the holobiont is facilitated by both the host genome and its associated microbial genome.

Moreover, genetic variation of the hologenome can be enhanced through transmission of different microbial symbiont populations that facilitate the optimum adaption to different environmental demands (e.g., changes in nutrition, stress, temperature). The hologenome theory may even account for complex biological phenomena such as certain behaviors. For instance, behavior that facilitates social interaction among holobionts might be considered evolutionarily adaptive/advantageous as it gives rise to greater transmission of microbiota, thereby enhancing genetic variation (Rosenberg et al., 2010; Rosenberg et al., 2009; Zilber-Rosenberg and Rosenberg, 2008). In light of these inextricable links between the microbiota and the brain throughout evolutionary history, it is imperative for the study of our own biology (and that of the entire animal kingdom) to understand how microbial symbionts influence brain physiology and behavior.

V. Studying the Microbiota-Gut-Brain Axis

Although we do not yet fully understand the functional significance of the symbiotic relationship between host and microbe especially in the context of brain health, a number of tools and animal models have been invaluable in allowing the scientific research community to constantly narrow the gaps in our understanding of the microbiota-gut-brain axis (see **Table 1**).

A. Germ-Free Models

GF animals (Bisgaard et al., 2011; Williams, 2014) have been invaluable tools for understanding microbe-host relationships (see **Table 2**). Lacking exposure to microorganisms since birth, GF animals provide insights into how the microbiota is integral in shaping the behavior, physiology, and neurobiology of its host (Weger et al., 2019).

In 1885, Louis Pasteur hypothesized that certain microbes were essential for the survival of complex life due

to the co-existence and co-evolution of micro- and macro-organisms (Pasteur, 1885). Yet in the post-World War II era, coinciding with the discovery of antibiotics, public distrust of bacteria evolved to a point where the dream of living GF increasingly appeared in fictional futuristic fantasies (Kirk, 2012). The concept of humans living in sterile worlds was even realized in 1971, when David Vetter was isolated in GF conditions as a newborn due to a severe combined immune deficiency and thus became known as the "Bubble Boy" (Kirk, 2012).

Perhaps the first reported GF animals were guinea pigs produced in 1897 via aseptic cesarean section (C-section) and kept free of microbes for two weeks (Nuttall and Thierfelder, 1987). However, successive generations of GF rodents were not produced until the mid-20th century (Gustafsson, 1946). Currently, similar methods are typically used to generate many generations of GF animals. To avoid inoculation of pups by microbiota, C-section is carried out carefully to avoid contact between pup and the microbes residing on both the dam's vagina and skin, and pups are then hand-raised in an aseptic isolator (Al-Asmakh and Zadjali, 2015; Gordon et al., 1966a; Luczynski et al., 2016a; Moya-Perez et al., 2017a; Stilling et al., 2014a). From this point on, colonies are maintained GF with sterile food, bedding, and water. Cages and feces are regularly swabbed to confirm that no bacteria are present (Bibiloni, 2012). Subsequent GF animals can then be bred in an isolator and GF pups born *per vaginum*. Alternatively, GF animals can be produced by embryonic transfer at the 2-cell stage into a GF host mother (Bibiloni, 2012).

Animals lacking microbiota have extraordinarily different development and physiology than animals hosting commensal bacteria, (see **Table 2** for a comprehensive summary of studies involving GF animals). GF animals are smaller in body weight and have impaired intestinal function (Aluwihare, 1971; Jeppsson et al., 1979; Savage et al., 1981), have lower concentrations of most gastrointestinal luminal amino acids than SPF mice (Yamamoto et al., 2018), and actually live longer (Gordon et al., 1966b; Reyniers and Sacksteder, 1958; Tazume et al., 1991; Wostman, 1968). Due to the lack of commensal microbes, GF animals have impaired immune systems, dysregulated hormone signaling, altered metabolism, and differences in neurotransmission from conventional counterparts (Kawase et al., 2017; Neufeld et al., 2011; Pan et al., 2018; Sudo et al., 2004; Weger et al., 2019). Interestingly, phenotypes of GF animals vary across species, sex, research group, and even strain, demonstrating that both microbiota and host genetics are important influencers of phenotype. For example, some studies involving GF Swiss Webster mice show a decreased anxiety-like behavior (Arentsen et al., 2018; Clarke et al., 2013; Neufeld et al., 2011) whereas the opposite has been found in male GF BALB/c mice (Chen et al., 2017b; Nishino et al., 2013).

Although an important tool, GF mice have many limitations in terms of aberrant physiology, neurodevelopment and immunity, as well as limited translatability to human situations (Nguyen et al., 2015). Nonetheless, they have been an important starting point in answering the question of whether the microbiota is involved in a given process or not (Luczynski et al., 2016a). Moreover, GF studies are now being extended to other non-rodent species including porcine models to enhance the translational value of findings (Charbonneau et al., 2016).

Alternatively, colonization of mice with specific, known strains of bacteria has also shown to be a useful approach to interrogate microbiota-physiology interactions (Gordon and Pesti, 1971). From these gnotobiotic animals, it is possible to decipher mechanisms of communication between specific members of the microbiota and the host organism. Among such approaches, the altered Schaedler flora (ASF) mouse line is most utilized (Lyte et al., 2019a; Orcutt et al., 1987; Wymore Brand et al., 2015). ASF mice are colonized with just eight bacterial species allowing a more simplified study of microbiota involvement in brain function relative to conventionally colonized strains, but with more clinical relevance than GF studies. The minimalist bacterial colonization of the ASF mouse avoids the complications of the high abundance and diversity in conventional mice, while overcoming the host developmental hurdles seen in GF mice, such as an underdeveloped immune system (Atarashi et al., 2011; Helgeland et al., 1996), slower intestinal epithelial turnover (Savage et al., 1981), differing nutritional requirements and less body fat (Backhed et al., 2004)., The ASF model thus presents an attractive alternative option for translational microbiota-gut-brain axis research, particularly involving stress (Lyte et al., 2019a).

B. Antibiotics

While initially developed to fight infections, antibiotics are also a useful pharmacological tool for investigating the impact of microbiota perturbations on brain and behavior (see **Table 3**). They offer much greater temporal flexibility and specificity compared to the GF model of microbiota ablation as they can be delivered acutely or chronically at any stage across an animal's lifespan (e.g., during periods of potential vulnerability such as the early postnatal period (Leclercq et al., 2017; O'Mahony et al., 2014), adolescence (Desbonnet et al., 2015), or in aging). Additionally, the ability to titrate the dose of antibiotics allows for a greater level of control over the extent of microbiota depletion, from minor perturbations to the microbiota through sub-therapeutic doses of a single antibiotic, to cocktails of antibiotics designed to substantially ablate the entire microbiota. An important consideration in the use of antibiotics to investigate the microbiota-gut-brain axis is their absorption from the GI tract. Non-absorbable antibiotics (i.e. vancomycin, neomycin, and bacitracin (Tochitani et al., 2016)) offer the advantage that they knockdown the microbiota in the gut while not entering systemic circulation, thereby avoiding any potential systemic and even central nervous system (CNS) effects and allowing us to directly assess the effect of a loss of a microbiota on the brain. Other antibiotics such as metronidazole and minocycline can potentially enter the central nervous system and can have direct action on brain and behavior (261) (e.g., microglial inhibition with minocycline; Riazi et al., 2015), so these results must be interpreted with caution. Despite such limitations, antibiotics have been crucial in corroborating the behavioral and biological observations documented in GF animals. Indeed, antibiotic administration to laboratory animals has been shown to influence behaviors such as sociability and anxiety (Degroote et al., 2016; Frohlich et al., 2016; Guida et al., 2018).

A final advantage of antibiotics is that they offer a tool to model the clinical scenario in humans. Administration schedules can be made to model the courses of antibiotics that millions of people take each year for multiple conditions, allowing us to determine the effect that such treatments may be having on the brain and behavior. The flexibility and translational relevance of antibiotics make them a hugely valuable tool in the study of the microbiota-gut-brain axis and they will form a key component of future studies in the field.

Table 3 summarizes the current state of knowledge regarding the impact of antibiotics on brain physiology and behavior.

C. Fecal Microbiota Transplant (FMT)

FMT is a procedure that involves the transfer of intestinal microbiota from one individual to another, commonly performed via oral administration of fecal material in rodents or colonoscopy in humans. When effective, this technique initially establishes a donor-like microbiome in the GI tract of the recipient, allowing stronger inferences to be made regarding the causal relationships between gut microbiota and host outcomes. The use of FMT in human medical treatment is gaining popularity, though it is not novel. Around 1,700 years ago, Ge Hong, a traditional Chinese medical doctor, documented the treatment of patients with food poisoning and severe diarrhea via oral administration of human fecal suspension (Zhang et al., 2012b). Later, in the 17th century, Italian anatomist Fabricius Aquapendente described bacteriotherapy using fecal flora in veterinary medicine (Brandt et al., 2012). 1958 marked the first documented use of FMT for therapeutic treatment of pseudomembranous colitis in humans (Eiseman et al., 1958; Han et al., 2016). Since that time, the FMT procedure has become most well-known for its remarkable success rate in the treatment of refractory *C. difficile* infection (CDI) (Han et al., 2016; Sekirov et al., 2010; van Beurden et al., 2017; van Nood et al., 2013). Moving from the clinic to the laboratory, FMT has opened up possibilities for more mechanistic investigations of the microbiota's role in various clinical conditions via "humanization" of the rodent microbiota.

Such studies have found that various behavioral phenotypes can be transferred by FMT, including anxiety-like behavior and aspects of depressive symptomatology, suggesting that gut microbiota are key components of regulating anxiety and depression (Bercik et al., 2011a; Bruce-Keller et al., 2015; Kelly et al., 2016; Zheng et al., 2016b). Furthermore, the composition of the gut microbiota has been linked to obesity and insulin resistance (Caricilli and Saad, 2014; Everard and Cani, 2013; Tai et al., 2015). GF mice were shown to have reduced body weight, and when conventionalized with normal intestinal microbiota, the animals experienced a 60% increase in body fat content and insulin resistance, combined with reduced food consumption (Backhed et al., 2004). Furthermore, the humanization of GF mice with microbiota from obese individuals resulted in a significant increase in body weight compared to individuals colonized with microbiota from lean individuals (Turnbaugh et al., 2006)Bacterial/genetics</keyword><keyword>Mice</keyword><keyword>Mice, Inbred C57BL</keyword><keyword>Mice, Obese</keyword><keyword>Obesity/*metabolism/*microbiology</keyword><keyword>Sequence Analysis, DNA</keyword><keyword>Thinness/microbiology</keyword></keywords><dates><year>2006</year><pub-dates><date>Dec 21</date></pub-dates></dates><isbn>1476-4687 (Electronic, illustrating that characteristics of the donor are important.

Typical FMT administration in non-GF rodents generally consists of treating the recipient with a cocktail of antibiotics, often provided via drinking water, followed by a single or repetitive oral gavage of inoculum consisting of donor fecal material over several days. Broad-spectrum antibiotics are often used to deplete existing microbiota and provide administered bacteria a less competitive environment in which to proliferate. Various studies use different combinations of antibiotic cocktails that

differ in concoction, concentration, and dosage time. Commonly used cocktails usually do not exceed a combination of five antibiotics at various individual doses and may include ampicillin, ciprofloxacin, neomycin, vancomycin, metronidazole, streptomycin and penicillin (Bruce-Keller et al., 2015; Ericsson et al., 2017; He et al., 2015; Kelly et al., 2016; Suez et al., 2014; Yano et al., 2015; Zhou et al., 2017). Antibiotic treatment time generally ranges from 3 days to 35 days, with a common treatment time of 1-2 weeks (Bruce-Keller et al., 2015; Ubeda et al., 2013; Yano et al., 2015; Zhou et al., 2017).

Some studies have shown successful transfer of the microbiota, even with no pretreatment of antibiotics, occasionally utilizing group housing of coprophagic animals, such as mice, to induce passive gut microbiota transfer, (Elinav et al., 2011; Manichanh et al., 2010; Stecher et al., 2010). However, a recent study compared three methods of FMT: pretreatment with antibiotics (ampicillin, neomycin, and vancomycin), pretreatment with bowel cleansing solution, and no pretreatment, all followed by three days of high-volume oral gavage, and found that pretreatment with antibiotics allowed for higher FMT efficacy (Ji et al., 2017). Interestingly, FMT can be achieved between different animal strains and species, including FMT from human to rodents (Kelly et al., 2016; Staley et al., 2017). Ultimately, utilizing GF animals as recipients of FMT provides an easier environment for introduced microbiota to colonize, and eliminates the potential need for antibiotic treatment prior to FMT but comes with the caveat that the GF animals are markedly altered before FMT (de Groot et al., 2017)

FMT is increasingly being utilized in humans for the treatment of CDI in the clinic (Cammarota et al., 2017) and, in a research setting, FMT has also been tested for the treatment of IBD, IBS, and chronic constipation. In a double-blind, randomized trial treating IBS with FMT, 65% of participants receiving FMT showed a response to treatment at three months, compared to 43% receiving a placebo (Johnsen et al., 2018). CDI is generally treated with antibiotics, but in the case of recurrent CDI, treatment with FMT ultimately cured 98% (Brandt et al., 2012). The potential of FMT in research and as a medicinal therapy provides promise for the treatment of GI-related diseases and conditions, including the practice of autologous FMT. Here, a patient is given an FMT of their own pre-surgery/ 'healthy' fecal matter during the recovery phase, effectively reconstituting their major commensal bacterial populations and reestablishing the patient's gut microbiota diversity as well as composition (Suez et al., 2018; Taur et al., 2018). This may well result in an increase in the practice of fecal matter banking for post-treatment recolonization of a patient's gut microbiota, a practice could become commonplace in the very near future.

D. Prebiotics and Fermented Foods

The definition of prebiotics as determined by the International Scientific Association for Probiotics and Prebiotics is "a substrate that is selectively utilized by host microorganisms conferring a health benefit" (Gibson et al., 2017). One of the main classes of prebiotics is dietary fiber, often defined as "carbohydrates with a degree of polymerization greater than 2, which fail to be hydrolyzed or absorbed in the small intestine" (Stephen et al., 2017). These include inulin, fructooligosaccharides (FOS), galactooligosaccharides (GOS), resistant starch and other soluble dietary fibers, amongst others (though not all dietary fibers are prebiotic). Typical dietary sources of prebiotics include fruits and vegetables such as asparagus, leek, banana, chicory, and grains such as oats and wheat. As Western-style diet consumption increases, a drop in prebiotic intake that correlates

with a rise in the incidence of inflammatory diseases, obesity, metabolic syndrome and anxiety, stress and other 'lifestyle' disorders have been seen. Importantly, prebiotics do not always change the composition and activity of the gut microbiota in a selective and predictable manner (Bindels et al., 2015). Nonetheless, prebiotic supplementation has been demonstrated to reduce stress-responsiveness, anxiety- and depressive-like behavior, as well as facilitate changes in hippocampal synaptic efficacy, including increased hippocampal brain-derived neurotrophic factor (BDNF) expression, general hypothalamic neuronal activity, and enhanced cognition and learning (see **Table 4**). Most studies thus far have been descriptive and are limited to demonstrating prebiotic influence on brain physiology and behavior (see **Table 4**). Further studies should, therefore, aim to understand the mechanisms by which prebiotics can affect brain physiology and behavior, with a specific focus on which gut microbial-derived metabolites are involved, and through which pathways these effects are mediated. Following is a more detailed description of different prebiotics currently in use.

Resistant Starch

Resistant starches (RS) are undigested carbohydrates and classified into four different types: the physically inaccessible RS1, a native granular starch consisting of ungelatinized granules called RS2, a retrograde amylose known as RS3 and the indigestible chemically modified RS4 (Haub et al., 2010). Different resistant starches have been shown to induce different changes in the gut microbiota composition in animal models (Lyte et al., 2016; Maier et al., 2017). One study has shown that rodents on a resistant starch diet demonstrated a reduction in exploratory behaviors in an open-field test (Lyte et al., 2016). Consumption of resistant starch for ten weeks significantly increased the abundance of *Ruminococcus bromii*, constituting 17% of total bacteria compared with 3.8% on the non-starch diet. Furthermore, individuals on a resistant starch diet showed an increase in relative abundance of uncultured *Oscillibacter* and *Eubacterium rectale* (Walker et al., 2011). A randomized study of 39 individuals found that a high resistant starch diet resulted in a significant increase in the Firmicutes:Bacteroidetes, along with an increase in the overall relative abundance of Firmicutes, alongside an increase in enzymatic pathways and metabolites associated with lipid metabolism in the gut (Maier et al., 2017). The Firmicutes:Bacteroidetes is a correlational and observational output of microbiome analysis that is currently somewhat informative based on the direction of change from a known starting or control point, where Firmicutes and Bacteroidetes represent over 99% of the known bacteria in the gut.

Inulin

Inulins are well-established prebiotics, which are predominantly found in a variety of fruits, vegetables and wheat. Numerous studies have shown that inulin can stimulate the growth of *Bifidobacterium* spp. and *Faecalibacterium prausnitzii,* while increasing butyrate production (de Preter et al., 2008; Kolida et al., 2007; Ramirez-Farias et al., 2009). Furthermore, administration of inulin to a dextran sulfate sodium-induced colitis mouse model resulted in an attenuation of the colitis symptoms in addition to an increase in *Lactobacillus* composition (Videla et al., 2001). Moreover, exposure to inulin/GOS prebiotic supplementation during pregnancy and lactation has been shown to bring about protection against food allergies with a decrease in histamine levels and intestinal permeability in the offspring (Bouchaud et al., 2016).

GOS and FOS

Galacto-oligosaccharides are well-established prebiotics known to be present in human milk (Barile and Rastall, 2013; Vandenplas, 2007). Infants fed formula supplemented with Bimuno-galactooligosaccharide (B-GOS®; Bimuno™, Clasado Biosciences Ltd, Buckinghamshire, UK), a proprietary product containing at least 65% GOS, had increased abundance of *Bifidobacterium* and *Lactobacillus* compared to unsupplemented infants, similar to levels reported in breastfed infants (Garrido et al., 2013; Vandenplas et al., 2014). Administration of B-GOS® in an elderly population reported a significant increase in *Bacteroides* and *Bifidobacterium* spp. with elevated levels of lactic acid in fecal water. Moreover, they also reported administration of B-GOS® resulted in a reduction in proinflammatory cytokines with an increase in both IL-10 and IL-8, anti-inflammatory cytokines (Vulevic et al., 2015). Studies have demonstrated a significant increase in pro-inflammatory cytokine with stress (Rea et al., 2016). However, administration of B-GOS® in mice attenuated post-inflammatory anxiety (Savignac et al., 2016). In addition, B-GOS® prevented a lipopolysaccharide (LPS)-mediated increase in cortical 1L-1β and 5-HT_{2A} receptor levels (Savignac et al., 2016). Administration of B-GOS® to individuals induced suppression of the neuroendocrine stress response and an increase in the processing of positive versus negative attentional vigilance, thus resulting in an early anxiolytic-like phenotype (Schmidt et al., 2015).

Fructo-oligosaccharide (FOS), are oligosaccharides known to be predominantly present in fruits. A double-blind intervention study in obese women with FOS showed an enhanced abundance in *Bifidobacterium* and *Faecalibacterium prausnitzii* (Dewulf et al., 2013). In a randomized, double-blind crossover study administration of FOS and GOS for 14 days showed significant increases in *Bifidobacterium* along with a reduction in butyrate-producing bacteria with adverse glycemic metabolism (Liu et al., 2017b). Administration of FOS-+GOS and GOS has been shown to reduce stress-induced corticosterone release, combined with a significant increase in cecal acetate and propionate concentrations, with a reduction in iso-butyrate levels. Moreover, mice fed FOS+GOS spent more time in the center of an open-field test, with an increase in the percentage of entries into the open area (Burokas et al., 2017), indicating a reduced anxiety phenotype.

H. Probiotics and Psychobiotics

Probiotics refer to candidate species of live bacteria that, when ingested in adequate amounts, confer beneficial health effects upon the host (Butel, 2014). Through interacting with the host microbiota and intestinal epithelium, probiotics have been shown to exert a wide range of effects upon host health, with various strains improving metabolism, immunity, endocrine function, and slowing aging in preclinical studies (El Aidy et al., 2015; Patterson et al., 2016). Although looking forward towards utilizing candidate probiotics for host health, we must acknowledge the potential impact that the inherent host diet and microbiota complexity can have on the probiotic itself, such as that seen recently with cumulative genetic mutations occurring to *E. coli* Nissle during passage through the murine gut (Crook et al., 2019). Perhaps the most intriguing effect of probiotics on the host is their modulation of brain physiology and behavior. *Faecalibacterium prausnitzii* (ATCC 27766) may function as a promising psychobiotic where it recently demonstrated an anxiolytic and antidepressant-like phenotype in rats, probably via increasing cecal SCFA and plasma IL-10 levels while reducing corticosterone and IL-6 levels (Hao et al., 2019). Considerable research over the last decade has documented how probiotics can influence various central neuronal processes such as neurotransmission, neurogenesis,

expression of neuropeptides, neuroinflammation, and even behavior (Sherwin et al., 2016b). Indeed, certain bacterial strains or cocktails of multiple bacteria have demonstrated efficacy in improving behavioral symptoms of various disorders from depression and anxiety to autism (see also Section VIII) (Allen et al., 2016; Bravo et al., 2011; Buffington et al., 2016; Hsiao et al., 2013; Kang et al., 2017; Savignac et al., 2014). These findings, (**summarized in Table 5**), have led to the concept of psychobiotics for the treatment of various neurological and psychiatric disorders through targeting of the gut microbiota (Dinan et al., 2013). Psychobiotics are now defined as microbiota-targeted interventions such as 'beneficial bacteria (probiotics) or support for such bacteria (e.g., prebiotics) that influence bacteria–brain relationships' (Sarkar et al., 2016). As the evidence to support the effects of psychobiotics on brain and behavior grows (Chong et al., 2019), the field is now turning to mechanistic studies in order to elucidate the biological underpinnings of psychobiotic effects.

I. Brain Imaging

The advent of human brain imaging techniques such as positron emission tomography in the 1980s allowed for conclusive demonstrations that alterations in the gut (e.g. by distension) lead to activation of key brain networks (Mayer et al., 2009; Van Oudenhove et al., 2007). Currently, studies that examine the interaction between gut microbes, brain and behavior in humans are limited. Magnetic resonance imaging (MRI) as a brain imaging tool became widely available in the early 2000s, with the field of neuroimaging reaching a stage where the once limited practical applications of structural and functional brain imaging have now become feasible to utilize, offering an ideal method of studying gut-brain interactions, *in vivo* (Mayer et al., 2015b)

Preclinical studies

A variety of different brain imaging techniques have been used to understand the microbiota-gut-brain axis. Using magnetic resonance spectroscopy (MRS), it has been shown that the bacterial strain *L. rhamnosus*-JB-1 was capable of increasing the neurotransmitter glutamate and its precursor glutamine in addition to N-acetyl aspartate and γ-aminobutyric acid (GABA) (Janik et al., 2016). Interestingly, the scale and timing of the response varied across the affected metabolites. In a recent study, diffusion tensor imaging was used to identify global changes in white matter structural integrity occurring in a diet-dependent manner in rats (Ong et al., 2018); although not surprising, microbiota analysis indicated changes in bacterial populations as a function of diet. By using a machine learning classifier for quantitative assessment of the strength of microbiota-brain region associations, changes in brain structure were found to be associated with diet-dependent changes in the gut microbiome.

Human studies

By combining human brain imaging techniques with neuropsychological measures, a landmark study investigated how ingestion of a fermented milk drink, combining four different bacterial strains, was able to affect brain function in healthy women (Tillisch et al., 2013). Alterations were observed in resting brain activity showing that ingestion of the fermented milk product was associated with changes in midbrain connectivity centered on the periaqueductal gray, along with other brain network regions including the prefrontal cortex (PFC), precuneus, basal ganglia, and the parahippocampal gyrus, which likely explain the differences ob-

served in activity during the tasks. Efforts have also been made to evaluate interactions among gut microbiota composition, brain microstructure, and a cognitive test (i.e., the Trail Making Test - an easily administered test that involves motor speed, attention, and cognitive flexibility) in obese (N=20) and non-obese (N=19) individuals (Fernandez-Real et al., 2015). The gut microbiota composition, specifically the abundance of the Actinobacteria phylum, of obese and non-obese subjects was linked with the cognitive testing scores, as well as alterations in neural activity in the thalamus, hypothalamus, and amygdala, suggesting that obesity affects the microbiota composition and subsequent cognitive performance (Fernandez-Real et al., 2015).

Two separate studies have investigated the association between IBS, changes in the microbiota, and brain-related alterations (Labus et al., 2017; Pinto-Sanchez et al., 2017b). An fMRI analysis showed that a *B. longum* strain reduced responses to negative emotional stimuli in multiple brain areas, including the amygdala and fronto-limbic regions, compared with placebo (Pinto-Sanchez et al., 2017a). Simply, the probiotic marginally reduced depression but not anxiety while increasing quality of life scores in patients with IBS, with improvements associated with changes in brain activation. The second study (Labus et al., 2017) investigated the relationship between brain region activation using fMRI, behavioral characteristics and microbiota composition in healthy women. The analyzed participants (N=39) were separated into two identifiable groups based on microbiota composition: a Prevotella-high group with 7 participants, and a Bacteroides-high group of 32 participants. Differential responses to negatively-valenced images were observed such that negative affect was associated with functional and structural differences in the right hippocampus within the *Prevotella* group. Although small scale, this is one of the first reports of behavioral and neurobiological differences related to microbial composition in healthy humans. It represents an exciting prospect for a better understanding of how differences in emotional, attentional, and sensory processing responses may be directed by the gut.

Brain imaging techniques have also begun to be used to explore the possible interactive role of gut microbiota and brain function in various neuropsychiatric disorders. For example, a recent study investigated both gut microbiota and choline concentrations in the anterior cingulate cortex in the prodromal stage of schizophrenia (He et al., 2018). Increased relative abundance of the orders *Clostridiales, Lactobacillales and Bacteroidales* were observed in fecal samples from individuals who were designated ultra-high-risk. Moreover, changes in the composition of gut microbiota indicated the increased production of short-chain fatty acid (SCFAs) which was coupled with increases in the levels of choline in the anterior cingulate cortex (He et al., 2018).

Preclinical studies have increasingly shown compelling evidence and consensus that microorganisms inhabiting the gut influence brain structure and function from birth and through the first years of life (Codagnone et al., 2018). In an essential first step in translating neonatal data into clinical neonatal populations, one group (Carlson et al., 2018) tested whether microbial composition at one year of age is associated with cognitive outcomes and fMRI measures. The investigators subtyped three different groups of infants based on their bacterial composition. Cognitive function at two years of age differed significantly between clusters. A higher α diversity was associated with lower scores on the overall composite score, and the visual reception scale, as well as the expressive language scale by two years of age, suggesting a slower rate of development. Ex-

ploratory analyses of neuroimaging data suggested that the gut microbiota had minimal effects on regional brain volumes at one and two years of age (Carlson et al., 2018).

Ongoing work in the field of brain imaging includes an approach to connect gut microbial ecology (Saulnier et al., 2011) with large-scale brain networks (Irimia and Van Horn, 2013). Such approaches will aid in our ability to determine how the microbiota influences brain function and potentially identify multiple mediators of the gut-brain axis. To date, the number of studies from which to draw a consensus is few, and further examination of the interaction between gut microbes, brain, and effect in humans is needed to inform preclinical reports that microbial modulation may or may not successfully influence cognitive function and subsequent behavior.

J. Techniques to Measure the Microbiome: Who is There and What are They Doing?

In microbiome research, answering these two headline questions (of who is there and what are they doing?) is central to investigating and understanding the dynamics not only within the microbiome but also between it and other systems, such as the brain. It involves the multi-collaborative efforts in both bioinformatic and sequencing approaches in tandem with biology and medicine.

Bioinformatics

The field of bioinformatics includes all work where computational algorithms are used to study biological phenomena (Luscombe et al., 2001; Ma, In Press). Generally, bioinformatics refers to biostatistics, data analysis, and computational biology. Due to the massive amounts of data that need to be processed when working with the microbiota, bioinformatics has played an important role in developing the field, and vice versa (Gevers et al., 2012; Hao et al., 2017). Indeed, endeavors such as the Human Microbiome Project (Group et al., 2009) and MetaHIT (Qin et al., 2010) have only been possible thanks to our rapidly improving capacity to handle big data(Ma, 2015). Fortunately, fields like ecology and statistics have dealt with comparable problems in the past, albeit often on a different scale (Gloor et al., 2017; Ma, 2015, In Press). Methods like multidimensional scaling and metrics such as diversity originate from these fields and are frequently used as powerful tools to analyze the microbiome, once they have been modified to suit microbiome data. Here, we will focus on the analysis of the microbiome, as well as alternate datasets like proteomics and metabolomics, which are often incorporated into microbiome analysis. For a review of metabolomics, metagenomics or transcriptomics, please see (Durack and Lynch, 2018), and see **Table 6**. (Gloor et al., 2017; Ma, 2015, In Press)

Microbiome Sequencing

Rapid improvements in sequencing technology have facilitated the development of two techniques that are integral to answering these questions: 16S sequencing and whole genome shotgun sequencing (Claesson et al., 2017). While the techniques are arguably similar, they are not mutually exclusive but provide complementary readouts that can inform each other (Clooney et al., 2016), see **Fig. 2**. A consequence of these

rapid improvements in sequencing technology has been a multitude of similar protocols that each have their own set of biases in their results. This makes pooling the data from two different studies more complicated (Clooney et al., 2016)Ribosomal, 16S/genetics</keyword><keyword>Sequence Analysis, RNA</keyword></keywords><dates><year>2016</year></dates><isbn>1932-6203 (Electronic. Recent efforts have been made to consolidate and standardize sequencing and analysis protocols, to improve overall quality and compatibility of research in the microbiome field (Knight et al., 2018; Mallick et al., 2017; Pollock et al., 2018).

16S amplicon sequencing

16S or amplicon sequencing represents a comparatively cheap way to measure the relative abundance of microbes present in a sample using next-generation sequencing technology. The idea behind the technique is to use PCR to amplify a highly conserved genetic sequence that is present in all bacterial members of the microbiota. These amplified sequences, or amplicons, can then be clustered based on their genetic relatedness and tallied to give an estimate of their relative abundance in a sample. While the technique can theoretically be performed using any amplicon, in practice, regions of the highly conserved 16S ribosomal RNA subunit are often used.

The relative composition of the microbiota on its own can be used to classify and differentiate samples. In addition, the popular bioinformatics tool PICRUSt (Phylogenetic Investigation of Communities by Reconstruction of Unobserved States) (Langille et al., 2013), along with Tax4Fun (Asshauer et al., 2015)Factual</keyword><keyword>Databases, Nucleic Acid</keyword><keyword>Genes, Bacterial/*genetics</keyword><keyword>Genetic Markers</keyword><keyword>Metagenome</keyword><keyword>Metagenomics/*methods</keyword><keyword>Phylogeny</keyword><keyword>RNA, Bacterial/genetics</keyword><keyword>RNA, Ribosomal, 16S/*genetics</keyword><keyword>Sequence Analysis, RNA/*methods</keyword><keyword>*Software</keyword></keywords><dates><year>2015</year><pub-dates><date>Sep 1</date></pub-dates></dates><isbn>1367-4811 (Electronic and Piphillin (Iwai et al., 2016), enable the prediction of the functional potential of the microbiota from 16S output by cross-referencing the identified microbiota with known genetic sequences (Langille et al., 2013). Thus, there is valuable information to be gained from 16S sequencing, although there are also important limitations. Firstly, 16S sequencing cannot identify novel microbial species nor account for intraspecies variation and mutations as the technique is restricted to genetic reference sequences that must be defined in a database *a priori*. Secondly, PCR introduces a bias in 16S tables, as some amplicon sequences will inevitably be amplified more efficiently than others (Acinas et al., 2005; Schloss et al., 2011) (Fig. 2).

Whole genome shotgun sequencing (WGS)

Whole genome shotgun sequencing (WGS) is more expensive and demanding on computational resources than 16S sequencing, but also capable of providing a strain level resolution of both microbiota abundance and functional capacity. In WGS, all DNA in a sample is isolated and sequenced using next-generation sequencing technology. After filtering out unwanted DNA (e.g., human DNA from a human stool sample), the remaining sequences can be used to either construct *de novo* genomes or align the sequences to a reference

database.

WGS offers several advantages over 16S (Clooney et al., 2016; Ranjan et al., 2016). Notably, there is usually no PCR amplification step in WGS, removing one source of bias. Furthermore, because the entire genome is sequenced, a much more reliable estimation can be made of the functional potential of the microbiome, and it is also possible to identify novel strains or mutations in a sample. Overall, the higher resolution of the information generated by WGS makes it possible to infer more about the microbiota in the sample.

Besides the cheaper cost, there are some situations where 16S is preferable to WGS. In samples that are heavily contaminated by off-target DNA (usually from the host, e.g., in biopsy samples), the signal of WGS can be too low for accurate measurement. Because 16S sequencing relies on the 16S subunit ribosomal RNA, which is unique to prokaryotes, most host contamination is not an issue. Furthermore, 16S sequencing can be performed when lower amounts of genetic material are available, which can be a key consideration when working with environmental samples like soil.

Metrics to Describe the Microbiome

Working with a highly complex ecosystem such as the microbiome, introduces many challenges, especially with regards to parsing a large amount of high-dimensional data into human-readable metrics. Fortunately, fields like ecology and statistics have dealt with comparable problems in the past, albeit often on a different scale. Methods like multidimensional scaling and metrics such as diversity originate from these fields and are frequently used as powerful tools to analyze the microbiome, once they have been modified to suit microbiome data (**Fig. 2**.). Perhaps the most important point to consider when analyzing microbiome data is that both 16S and WGS produce compositional data, data that contains information about the ratios between parts of the whole, but never contains information about absolute counting numbers (Aitchison, 1986). Many of the properties of compositional data are distinct from those of classical datasets and classical statistical tools such as Pearson's correlation coefficient are often not appropriate (Pearson, 1897). Fortunately, compositional data analysis is a well-studied and documented field of statistics (Aitchison, 1986). Recently, great efforts have been made to apply compositional data analysis techniques to the microbiome field (Gloor et al., 2017)J. M.</author><author>Pawlowsky-Glahn, V.</author><author>Egozcue, J. J.</author></authors></contributors><auth-address>Department of Biochemistry, University of Western Ontario, London, ON, Canada.
Departments of Computer Science, Applied Mathematics, and Statistics, Universitat de Girona, Girona, Spain.
Department of Applied Mathematics, Universitat Politecnica de Catalunya, Barcelona, Spain.</auth-address><titles><title>Microbiome Datasets Are Compositional: And This Is Not Optional</title><secondary-title>Front Microbiol</secondary-title></titles><periodical><full-title>Front Microbiol</full-title></periodical><pages>2224</pages><volume>8</volume><edition>2017/12/01</edition><keywords><keyword>Bayesian estimation</keyword><keyword>compositional data</keyword><keyword>correlation</keyword><keyword>count normalization</keyword><keyword>high-throughput sequencing</keyword><keyword>microbiota</keyword><keyword>relative abundance</keyword></keywords><dates><year>2017</year></dates><isbn>1664-302X (Print.

Comparative relative abundance

The most straightforward method of comparing two samples is to compare the presence of specific microbes. It should be noted that because of the nature of the output of both 16S sequencing and WGS, it is very rare to be able to work with absolute counts of organisms. Rather, relative abundance is used to compare samples. This is an important point since relative abundance can change in situations where absolute levels may not, and vice versa

Diversity

Going one level further than comparative relative abundance, microbiome diversity can be used to quantify the degree of heterogeneity within a sample or the difference between two samples. There are many different formulas that produce diversity metrics, all of which can be categorized into three closely related classes: α, β and γ diversity (Tuomisto, 2010a, b). α-diversity describes the diverseness within a sample, while β-diversity describes the diversity, or dissimilarity, between samples (Tuomisto, 2010a). γ-diversity is rarely used and describes the total species diversity over all samples, comparable to α-diversity in a single sample. Different formulas for diversity lay different weights on factors like the *richness* of a sample in terms of the number of different species represented, or the *evenness* of the distribution of the species in a sample. It can often be valuable to calculate diversity using several different metrics, depending on the research question.

Principal component analysis (PCA)

A common way to visualize high-dimensional data, like relative abundance, is by applying a multidimensional scaling (MDS) algorithm. Principal component analysis (PCA) is both common and appropriate in microbiome research, but other algorithms are available and sometimes useful. In PCA, the distances between every combination of two points in a set are taken as an input, and a set of coordinates is generated as an output. These coordinates can be used to plot each sample as a point in 2-dimensional or 3-dimensional space, using the principal coordinates as the axis. On the plot, points that are closer together represent samples that are more similar in composition.

Functional metagenomics

The analysis of function represents a high-level readout of the microbiome that can give insight into the effect or consequence that a change in the microbial community can have on its host. Functional metagenomics are often a product of either WGS or the application of functional prediction tools on 16S datasets. The reliability of functional analysis depends on the availability of high-quality curated data on the metagenome in question (Heintz-Buschart and Wilmes, 2018). Promisingly, the classical ecology concept of functional “guilds,” groups of taxonomically distinct but functionally related organisms, has been proposed to apply to the microbiome (Zhao et al., 2018).

Robustness

Recently, robustness has been explored in the context of the microbiome (Eng and Borenstein, 2018). Robustness as a metric expresses information about the degree of change a community will undergo after a perturbation and how fast and to what degree it can recover, if at all. Robustness highlights an interesting aspect of complex ecosystems. For example, a species, or clade (a branch of a phylogenetic/ contextual tree), can have little or no effect on its environment by itself but plays an important role in the maintenance of a steady state. This phenomenon is known in ecology as a keystone species, whereby the disappearance of that species will cause the ecosystem to drastically change or even collapse (Mills et al., 1993).

In Silico Models of the Microbiome

Although human and animal models have many advantages, there are numerous situations where the specific constraints of an *in vivo* model can over-complicate an experiment. In cases like this, *in silico* models of the microbiome can be utilized. Metabolic models of the microbiome, often utilizing our growing capacity to produce, process and handle big data, have yielded invaluable understanding in microbe-microbe interactions and microbe-environment interactions (Magnusdottir and Thiele, 2018; Sung et al., 2016). For instance, Flux Balance Analysis (FBA) models have been used to predict and understand the behavior of microbes given their environment (Orth et al., 2010; Thiele et al., 2013; Zelezniak et al., 2015). The generation and refinement of genome-scale metabolic reconstructions (GENREs) is essential for realistic modeling of these types of interactions, which will be facilitated by the recent publication of a large database containing 773 high-quality human gut GENREs (Magnusdottir et al., 2017). *In silico* models of the microbiome can be used not only to answer experimental questions but also to verify the reliability of the results. One of the current limitations of the field is the difficulty in finding a gold standard dataset with which to validate statistical models for microbiome data. Often, there is no sufficiently large dataset of the required type available. However, synthetic datasets, generated by programs like SparseDOSSA (Human Microbiome Project, 2012), can be used to tackle this problem by generating realistic samples from a completely known and controllable source. Hopefully, with the development of evermore powerful computing technologies, and intricately designed programming suites, *in silico* modeling will increasingly complement the necessary use of animal models in fundamental microbiome research.

VI. Microbiota-Gut-Brain Axis across the Lifespan

As stated earlier the microbiota has been our constant companion in life throughout evolutionary history. This rich ecosystem is not static, but rather is in a constant state of flux across the lifespan. Within individuals, small day-to-day variations in microbiota composition are generally observed (Costello et al., 2009), but these fluctuations become most obvious when we take a wider view across the lifespan (see **Fig. 3**). At both extremes of life, the microbiota is characteristically different from the typical adult gut microbiota in both levels of diversity and representation of specific taxa (Claesson et al., 2012; Salazar et al., 2014; Yatsunenko et al., 2012). It has been hypothesized that these periods of transformation in the microbiota may be likened to sensitive periods, during which the microbiota is not only responsive to external influences (and therefore amenable to treatment) but also highly influential with regards to the overall health of the host (Borre et al.,

2014; Gensollen et al., 2016; Gur et al., 2015). In the neuroscience literature, a sensitive period is defined as a developmental time window during which the brain is more sensitive/vulnerable to environmental inputs (Hensch, 2005). Originally applied to the development of different sensory systems, sensitive periods are now being investigated for higher order behaviors as well, such as language development and cognition (Callaghan et al., 2013; Hensch and Bilimoria, 2012; Werker and Hensch, 2015). It is likely to be biologically relevant that sensitive periods in the microbiota align with sensitive periods in the development or decline of other bodily systems; this includes, but is not limited to, the innate immune system, the hypothalamic-pituitary-adrenal (HPA) axis, and brain development in general (Borre et al., 2014; Gensollen et al., 2016; Goyal et al., 2015). In this section, we discuss three broad sensitive periods – early-life, adolescence, and aging – and examine the role of the microbiome in determining host brain function during these critical windows.

A. Early Life

There is some controversy about when the human GI tract is first colonized, with recent studies reporting the existence of a placental microbiota and *in utero* colonization of the fetus (Aagaard et al., 2014; Collado et al., 2016; Jimenez et al., 2008), while others suggest that this evidence is limited by a lack of contamination controls (Lauder et al., 2016; Lim et al., 2018; Perez-Munoz et al., 2017; Theis et al., 2019), maintaining that the placenta and womb are sterile (Kim et al., 2017; Lauder et al., 2016; Lim et al., 2018; Milani et al., 2017; Perez-Munoz et al., 2017). If *in utero* colonization does occur, it seems to have a limited effect on the early postnatal microbiota composition relative to the initial seeding of the microbiota during birth (either by Cesarean section or *per vaginum*; see **Section VI. B**). This is not to discount the potential impact of prenatal transfer of even small numbers of bacteria and other microorganisms from the mother to the infant. As stated earlier, GF mice, which have never had microbial colonization, (but see: (Hornef and Penders, 2017), have been invaluable tools in parsing the role of the microbiota in gut-brain signaling across the lifespan (Luczynski et al., 2016a); see **Section II.A**, and **Fig. 1**). Indeed, GF status during pregnancy has dramatic effects on offspring development in rodents. For example, the blood-brain barrier (BBB) typically develops around the second week of embryonic life, with permeability decreasing sharply at approximately embryonic day 15 in the mouse (Braniste et al., 2014). However, GF mouse embryos exhibit increased BBB permeability and low expression of the tight junction protein occludin on embryonic days16-18, effects that were maintained postnatally and into adulthood (Braniste et al., 2014). Importantly, this study identified that BBB integrity could be restored by postnatal recolonization of the microbiota, implying a causal role for the microbiota in ensuring development of the BBB. Aside from maternal GF status, other prenatal maternal factors such as diet, obesity, immune activation, and stress, all of which are known to alter offspring mental and physical health outcomes, have also been found to influence offspring microbiota composition in rodents and/or humans (Buffington et al., 2016; Galley et al., 2014; Hsiao et al., 2013; Jasarevic et al., 2017; Rincel et al., 2019; Sugino et al., 2019; Zijlmans et al., 2015).

As for all stages of life, it is difficult to give a strict definition of what constitutes a healthy microbiota during early life. However, it is known that the microbiota tends to follow one of a few trajectories of development, with early-colonizing species shaping the long-term composition (Martinez et al., 2018). Soon after birth, the microbiota is typically characterized by relatively high abundances of *Enterobacteriaceae*, *Bifidobacteriaceae,*

and *Clostridiaceae*, but low levels of *Lachnospiraceae* and *Ruminococcaceae* at the family level (Bokulich et al., 2016; Chu et al., 2017; Yassour et al., 2016). As the infant matures, strict anaerobes gradually take over as the dominant taxa, and there is an increase in overall diversity to adult-like levels by around 1-3 years of age, coinciding with weaning and a shift to solid food intake (Koenig et al., 2011; Palmer et al., 2007; Yatsunenko et al., 2012). This rapid development at weaning is observed across species and was recently shown to be critical for protection against later development of immunopathology in mice (Al Nabhani et al., 2019). However, even after weaning, the microbiota continues to change (Al Nabhani et al., 2019). The composition and function of the microbiota in healthy children (measured at 7-12 years of age) remains significantly different from the healthy adult microbiota (Hollister et al., 2015). In particular, the gut microbiota of children is functionally enriched in pathways supporting ongoing development (e.g., genes involved in vitamin synthesis and de novo folate synthesis, anti-inflammatory pathways; Hollister et al., 2015).

The infant and child microbiota is susceptible to a range of environmental influences, from birth mode (vaginal vs C-section), and birth location (home vs hospital) , to diet, (including breastfeeding versus formula feeding) (Azad et al., 2013; Biasucci et al., 2010; Dominguez-Bello et al., 2010; Ho et al., 2018), maternal gestational diet and weight gain (Baumann-Dudenhoeffer et al., 2018; Seppo et al., 2019), pet ownership (Azad et al., 2013; Tun et al., 2017), physical illness (Combellick et al., 2018; Kan et al., 2019), antibiotic use (Korpela et al., 2016; Yassour et al., 2016), and stress (Gur et al., 2015; Rincel et al., 2019; Zhong et al., 2019; Zijlmans et al., 2015). Although some of these factors exert a diminishing influence on the microbiota over time (e.g., the effects of birth mode on microbiota composition are no longer apparent by 6 weeks of age; Chu et al., 2017; Hill et al., 2017), these early life factors may still have long-lasting implications for the physical and mental health of the individual (Callaghan et al., 2019; Gensollen et al., 2016; Milani et al., 2017), consistent with the idea that there are sensitive periods for microbiota-gut-brain interactions. Longitudinal studies testing this hypothesis are currently limited, but emerging research in both humans and rodents suggests that early-life microbiota manipulations can alter trajectories of physical and mental health or cognitive performance.

In humans, the currently available evidence for enduring effects of early-life microbiota changes on host physiology and brain health, although moving more towards mechanism and causation, is largely correlational. The evidence supports a link between early-life microbiota composition, or antibiotic use, and later metabolic and immune function (specifically overweight/obesity and asthma/allergy; Abrahamsson et al., 2014; Azad et al., 2014; Penders et al., 2007; Sjogren et al., 2009; Stanislawski et al., 2018a; Sugino et al., 2019). Correlations have also been observed between childhood microbiota composition and behavioral temperament (Christian et al., 2015), functional activity/connectivity in the brain (Callaghan et al., 2019; Gao et al., 2019), and cognitive function (Carlson et al., 2018). Beyond correlation, preliminary clinical trials of probiotic interventions for at-risk children have yielded promising results with regards to reducing risk for GI problems (Indrio et al., 2014; Weizman et al., 2005), sepsis (Panigrahi et al., 2017), and even autism spectrum disorder (ASD) (Parracho et al., 2010; Partty et al., 2015) and attention deficit hyperactivity disorder (Partty et al., 2015), although a recent study of post-natal probiotics (*L. rhamnosus* HN001 or *B. animalis* HN019) found no effect of either strain on later neurocognitive outcomes (Slykerman et al., 2018). Such investigations are becoming more widespread based on strong preclinical evidence that early-life disruption of the microbiota alters a wide range of behavioral and neural outcomes both during development and later in life (Clarke et

al., 2013; Diaz Heijtz et al., 2011; Leclercq et al., 2017; Minter et al., 2017; O'Mahony et al., 2014; Olszak et al., 2012; Stilling et al., 2015). Preclinical research also provides cause to focus on early-life microbiota interventions. Several groups have now shown that early probiotic interventions mitigate the effects of antibiotic-treated and C-section delivered infants, early-life stress, maternal high-fat diet, and maternal immune activation on infant outcomes (see **Table 5**) (Buffington et al., 2016; Callaghan et al., 2016; Cowan et al., 2016; Fukui et al., 2018; Gareau et al., 2007; Hsiao et al., 2013; Korpela et al., 2018).

B. Adolescence

Adolescence has been labeled a time of "storm and stress," reflecting the unique challenges associated with this stage of life (Hall, 1904). In addition to the well-known hormonal fluctuations that occur during adolescence, the brain undergoes vast re-shaping, including pruning, myelination, volumetric changes in various regions and changes in functional connectivity (Blakemore, 2012; Blakemore and Choudhury, 2006; Casey et al., 2008; Spear, 2000) (Fig. 3). Rapid physical development of the body and brain coincides with dramatic shifts in social networks (notably increased independence from caregivers), diet, sleep patterns, and exposure to alcohol and drugs. Faced with this cocktail of stressful new experiences on a background of unstable hormones and altered brain function, it is perhaps unsurprising that adolescents are vulnerable to mental health problems (Kessler et al., 2005; Lee et al., 2014; Paus et al., 2008). Given that all of these factors have been linked to alterations in the microbiota-gut-brain axis in adults, exploration of the microbiota during the sensitive period of adolescence has the potential to provide both insights and interventions to improve adolescent well-being (Flannery et al., 2019; McVey Neufeld et al., 2016a; McVey Neufeld et al., 2016b).

There have been very few studies directly comparing the adolescent and adult microbiota in humans. In a small cohort (*n* = 22) of healthy 11-18-year-old adolescents, a correlation between age and microbiota composition was observed such that older adolescents were more similar to (but generally still separate from) the adult microbiota profile (Agans et al., 2011)Bacterial/genetics</keyword><keyword>Female</keyword><keyword>Genome, Bacterial</keyword><keyword>Humans</keyword><keyword>Intestines/*microbiology</keyword><keyword>Male</keyword><keyword>*Metagenome</keyword><keyword>Middle Aged</keyword><keyword>Oligonucleotide Array Sequence Analysis</keyword><keyword>Polymerase Chain Reaction</keyword><keyword>Principal Component Analysis</keyword><keyword>Young Adult</keyword></keywords><dates><year>2011</year><pub-dates><date>Aug</date></pub-dates></dates><isbn>1574-6941 (Electronic. At the genus level, adolescents had higher relative abundances of *Bifidobacterium* and *Clostridium*, but lower relative abundances of *Prevotella* and *Sutterella*. These differences are similar to those reported in other studies of the child microbiota (Hopkins et al., 2001), indicating that there is a gradual transition from childhood to adulthood rather than a distinct adolescent profile, although further work is needed to confirm this result. Initial reports show that certain features of the microbiota correlate with both diet and metabolic outcomes in adolescent populations (Del Chierico et al., 2018; Jang et al., 2017; Stanislawski et al., 2018b), suggesting that more in-depth analyses of the functional relevance of the microbiota in adolescence are warranted. This pursuit would be aided by more preclinical studies in this area as there is a paucity of research addressing the question of age-specificity. In rodents, it has been shown that sex differences in the microbiota emerge only after puberty onset (Markle et al., 2013) and that

probiotic treatment during a period of early-life stress reverses stress-induced changes in the timing of puberty onset (Cowan and Richardson, 2018). Further, long-term antibiotic-induced depletion of the microbiota from adolescence alters adult cognition, social behavior, and anxiety (Desbonnet et al., 2015). This chronic treatment also reduced central levels of BDNF, oxytocin and vasopressin and altered tryptophan metabolism in adulthood. While this particular study did not provide clarity with regards to the idea that adolescence is a sensitive period (because the treatment continued into adulthood and no adulthood-only treatment was included). However, there are now a number of reports that early-life microbiota interventions are more efficacious when directly compared to the same interventions administered in adulthood (Buffington et al., 2016; Diaz Heijtz et al., 2011; Ellekilde et al., 2014; Olszak et al., 2012; Sudo et al., 2004). Overall, this work provides further support for the existence of early-life sensitive periods of microbiota-gut-brain interaction for at least some behavioral and neural outcomes.

C. Aging

Aging is a slow process of deterioration of various homeostatic functions accompanied by an increased prevalence of disease (Lopez-Otin et al., 2013). The United Nations defines 'older persons' as those over 60 years of age, which roughly translates to 20 months in a rodent model (Prenderville et al., 2015). Distinct hallmarks of aging are apparent from the genetic level (genomic instability, epigenetic alterations, telomere attrition) to the cellular level (mitochondrial dysfunction, cellular senescence, stem cell exhaustion, oxidative stress, altered proteasomal activity and autophagy), including an imbalance of key messengers (decline in growth factors, neurotransmitter imbalance, dysregulated immunity) and altered receptor sensing (altered stress axis activity, deregulated nutrient sensing), ultimately disrupting the homeostasis of the aging organism (Lopez-Otin et al., 2013) (Fig. 3.). Aging is also associated with changes in gut physiology, including hypochlorhydria, gastric motility disorders, and degenerative changes in the ENS, yielding dramatic effects on the composition and function of the gut microbiome (Konturek et al., 2015).

While the composition of the adult human gut microbiota is generally stable if unperturbed, its stability deteriorates in old age (Claesson et al., 2011). Diet and physical activity, two factors that generally decline in later life, can dramatically affect well-being, cognitive performance, and the microbiota at any stage of life, but their effects seem to be exaggerated in older individuals (Vauzour et al., 2017). Aside from this loss of stability, or perhaps because of it, characterization of the aging gut microbiome has proven difficult. First, the timing of the transition to an "elder-type" microbiome is not as clearly demarcated as the shift from an infant-type to an adult-type microbiome. Furthermore, while comparisons of adult and elderly individuals have identified clear differences in the microbiota composition between these two groups, the differences between studies have been sizable, perhaps due to cultural, geographical or methodological variances (Biagi et al., 2016; Biagi et al., 2017; Claesson et al., 2012; Mueller et al., 2006; Odamaki et al., 2016; Salazar et al., 2017; Shen et al., 2018). Decreasing diversity of the gut microbiota, generally associated with adverse outcomes in adults, has been linked to aging (Biagi et al., 2010) and age-related impairments like frailty in humans (Claesson et al., 2012; Jackson et al., 2016). In contrast, aged (24-month old) mice have been shown to exhibit increased diversity compared to younger adult mice (Scott et al., 2017). In terms of specific taxa, some studies have observed a decrease in beneficial *Lactobacillus* and *Bifidobacterium* in aging (Hebuterne,

2003). A reduced Firmicutes:Bacteroidetes ratio has been reported in Irish and French elderly compared to young adults (Claesson et al., 2011; Mariat et al., 2009), although this effect was not observed in a comparison of Italian centenarians, elderly and young adults (Biagi et al., 2010). Studies in semi-supercentenarians (people between 105-109 years of age) have found specific taxa such as *Akkermansia* to be more abundant, suggesting distinct gut microbiota changes at this extreme of life might be promoting healthy aging and longevity (Biagi et al., 2016; van der Lugt et al., 2018), as well as restore intestinal permeability and subsequent immunomodulation in aged mice (Bodogai et al., 2018).

Despite difficulties in identifying consistent aging-related compositional changes in the microbiota, further evidence supports the hypothesis that the microbiota plays a functional role in (un)healthy aging. A recent study demonstrated that that suppression of the gut microbiome using broad-spectrum antibiotics restored arterial function in old mice (20-24 months old) to levels observed in young animals (8-10 weeks old), which was coupled with normalization of both oxidative stress and inflammation (Brunt et al., 2019). Earlier studies in rodents demonstrated that GF mice live longer than conventional controls, linking gut microbiota to the decline of immune system function, or senescence (Glimstedt, 1959; Gustafsson, 1946). More recently in a human population, the ELDERMET study reported breakthrough research in which age-related shifts in gut microbiota composition were linked to various functional health measures, including frailty, cognition, depression, and inflammatory markers (Claesson et al., 2011; Claesson et al., 2012). For example, one study found that the more diverse the diet, the more diverse the microbiota, which was linked to improved health and reduced frailty (Claesson et al., 2012). Specific microbial taxa are also associated with reduced frailty in elderly populations, including *Bacteroidetes* (Bartosch et al., 2004; Hopkins et al., 2001; van Tongeren et al., 2005), *Clostridium cluster XIVa* and *Faecalibacterium prausnitzii,* one of many butyrate-producing bacteria with anti-inflammatory properties (Bartosch et al., 2004; van Tongeren et al., 2005; Zwielehner et al., 2009). In contrast, the bacterial family *Porphyromonadaceae* has been linked to declines in cognition and affective disorders (Bajaj et al., 2012; Collins et al., 2012). This nicely parallels results in a preclinical study showing that aged mice have a higher relative abundance of *Porphyromonadaceae* and that the levels of this family correlate with increased anxiety-like behavior (Scott et al., 2017).

Altered aged gut microbiota compositions have also been proposed to contribute to “inflammaging” (Thevaranjan et al., 2017), the heightened proinflammatory status and decline in adaptive immunity progressively expressed in older age (Franceschi et al., 2000). Inflammaging contributes to the speed of the aging process and may progress the development of age-related diseases (Xia et al., 2016), from neurological disorders like Alzheimer’s disease (Giunta et al., 2007) to metabolic and other physical disorders like heart disease, osteoporosis, and type II diabetes (Boren and Gershwin, 2004; Franceschi et al., 2001; Lencel and Magne, 2011). Both aging and stress weaken the integrity and function of the GI barrier (Kelly et al., 2016; Thevaranjan et al., 2017) and negatively affect BBB permeability (Esposito et al., 2002; Montagne et al., 2015) potentially accelerating inflammaging. By utilizing various models targeting the gut microbiome including pre-, pro- and postbiotics recent studies have shown a role for the gut microbiome in regulating neuroimmunity from middle- to old age which have implications for therapeutic interventions combatting age-related neurodegeneration and cognitive decline (Boehme et al., In Press; Fonken et al., 2018; Matt et al., 2018). One prebiotic study examining the effect of diets differing in sugar, fat, and fiber content on the gut microbiota

of mice humanized with microbiota from healthy or frail older people, reported that the frailty-associated gut microbiota did not reciprocally switch to a younger healthy-subject like state (Tran et al., 2019). Further, supplementation with prebiotics was associated with fewer detected effects in humans than diet adjustment in animal models (Tran et al., 2019).

Further evidence of a link between the microbiota and inflammaging comes from studies showing compositional changes in the microbiota that occur with age induce subclinical intestinal inflammation in elderly individuals with a high incidence of chronic disease (Guigoz et al., 2008), while reduced levels of *Akkermansia* following FMT from old mice into young GF mice was associated with an inflammaging phenotype in the recipient young mice (Fransen et al., 2017). An important component of the immune system and potential contributor to inflammaging are microglia, which are the brain's resident immune cells. As key players in the brain's immune orchestra, microglia shape neuronal wiring and activity, synaptic plasticity, phagocytosis and support the survival of neurons and neuronal progenitors via the secretion of growth factors (London et al., 2013; Tay et al., 2017) (see **Sections IV C., E., and V**). However, during aging, microglia develop into a highly reactive and unbalanced state promoting cognitive dysfunction including altered brain plasticity and neurodegeneration (Boehme et al., 2014; Lui et al., 2016; Tay et al., 2017; von Bernhardi et al., 2015). Recent studies have shown that GF mice display deficits in microglia maturation and function, while recolonization or administration of key gut microbiota metabolites such as SCFAs restore microglial function (Erny et al., 2015). Such studies suggest that targeting microglia could present an interventional approach to ameliorate neurodegenerative disease (Boehme et al., In Press; Matt et al., 2018).

Indeed, administration of microbiota-targeted diets to prevent the age-associated decline of beneficial *Bifidobacterium* has been found to have positive effects on gut microbiota composition and associated health. A recent study found that a 14-week long dietary intervention with prebiotics increased both *Bifidobacterium* and *Akkermansia* in middle-aged mice (Boehme et al., In Press). Moreover, the abundance of *Bifidobacterium* strongly correlated with genes involved in colonic health in the early phase of aging (van der Lugt et al., 2018). Similarly, *Bifidobacterium* species have been shown to be negatively correlated with pro- and anti-inflammatory cytokine levels in humans indicating that modulation of Bifidobacteria may represent a target for reducing the inflammatory response (Ouwehand et al., 2008).

Thus far, dietary restriction has been the most effective strategy to demonstrate an increase in lifespan across a whole range of investigated species, including nonhuman primates (Colman et al., 2009; Fontana et al., 2010; Fraumene et al., 2018; Lin et al., 2002; Mattison et al., 2012; Rusli et al., 2018; Zhang et al., 2013). This, once again, highlights diet as a key determinant of healthy aging, possibly via modulation of the gut microbiota. Studies in rodents support this interpretation, finding that short-term to life-long caloric restriction leads to structural changes of the gut microbiota (Fabbiano et al., 2018; Fraumene et al., 2018; Zhang et al., 2013) with the genus *Lactobacillus,* amongst others, positively correlated with lifespan (Zhang et al., 2013) and accompanied with changes in microbial metabolite production such as SCFAs (Tanca et al., 2018). Moreover, an intriguing FMT study in the short-living killifish showed that exchange of microbial communities from young to old increased longevity in the older group (Smith et al., 2017). This illustrates the potential for gut

microbiota modulation as a therapeutic strategy to benefit an aging host.

VII. Pathways of Communication

There are many pathways of potential communication between the gut microbiota and the brain, from intricately innervated and highly modifiable neuronal pathways to incredibly subtle and difficult to measure small molecule messaging systems, both locally in the gut and distally in the brain. In the following section, we will introduce many of these communication methods (Fig. 4.). However, much work is needed to fully resolve the exact mechanisms as to how bacteria in the lumen of the gastrointestinal tract can exert such marked effects on brain and behavior.

A. Autonomic Nervous System (ANS)

The autonomic nervous system (ANS) is a neural relay network, with neurons located within the central and peripheral nervous systems, controlling bodily functions without conscious effort (autonomously), such as breathing, heartbeat and digestion. The ANS is comprised of the sympathetic and parasympathetic branches. Combined with activity from the ENS and modulation by the CNS, the ANS is responsible for physiological homeostasis, as well as responding to endocrine, motor, autonomic, and behavioral areas. The individual components of the microbiota-gut-brain axis communicate with each other bi-directionally, both antagonistically and synergistically, within the ANS (Mulak and Bonaz, 2004). In combination with the HPA axis, the ANS comprises a vast and complex network of integrated communication between the brain and the gut, involuntarily establishing and regulating host physiological homeostasis (Janig, 2006). The ANS, in combination with neuronal and neuroendocrine signaling, can induce CNS-modulated changes in the gut (top-down effects) (Mayer et al., 2015b). Key GI functions such as gut motility and permeability, epithelial fluid maintenance, luminal osmolarity, secretion of bile, carbohydrate levels, mechanical distortion of the mucosa, bicarbonate and mucus production as well as the mucosal immune response and intestinal-fluid handling, are all controlled by the ANS (Wehrwein et al., 2016).

Incoming visceral information from the gut via the ANS is processed by the CNS, which then directs responses essential for survival. Further processing of this information involves positive and negative feedback loops which act on peripheral organs (Bonaz and Bernstein, 2013). The ANS provides the gut with the most direct neurological response available, leading to rapid changes in gut physiology, through innervation of the target organ, in both health and disease (Bienenstock et al., 2015), such as with the pain response (Mayer and Tillisch, 2011), and stress (Ulrich-Lai and Herman, 2009).

Direct or indirect ENS-microbiota interactions can occur as a result of ANS activity. The sympathetic and parasympathetic systems can influence ENS neurocircuitry, resulting in changes in motility which can affect the rate of delivery of pre and pro-biotics to the small intestine and colon, including resistant starches and dietary fibers, and other critical microbial nutrients (Maier et al., 2017). Local GI autonomic activation can be triggered by interoceptive afferent feedback from the gut as well as CNS cognitive and emotional efferent

modulation (Mayer and Tillisch, 2011).

Microbes can communicate with each other via metabolites, similar to those recognized by host cells and can thereby interact with gut ANS synapses (Rhee et al., 2009). Microbiota-derived neuromodulatory metabolites include tryptophan precursors and metabolites, serotonin (5-hydroxytryptamine, 5-HT), GABA and catecholamines (Fig. 4.). Multiple research groups (Chey et al., 2001; Hsiao et al., 2013; Lyte, 2013; Sokol and Adolph, 2018; Wall et al., 2014) have demonstrated that the microbially-modulated metabolite 4-ethylphenylsulfate is sufficient to induce anxiety-like behavior in mice. Indeed, the gut microbiota has been shown to modulate locomotor activity in *Drosophila,* probably via bacterial-derived metabolites (Schretter et al., 2018), (Chen et al., 2019). Further, vagal sensory neuron activation via *Campylobacter jejuni* gut inoculation of mice resulted in direct activation of the neuronal activation marker c-Fos in the vagal sensory ganglia and the primary sensory relay nucleus for the vagus nerve, the nucleus tractus solitarius (NTS) in the medulla oblongata (Goehler et al., 2005). These findings indicate that gut autonomic nerves carrying sensory information that can signal directly to the brain upon local GI microbial metabolite stimulation.

Sympathetic gut innervation involves subclasses of postganglionic vasoconstrictor as well as secretion and motility suppressing neurons. Altered neurophysiology of sympathetic innervation results in altered GI transit, motility and secretion, primarily via modification of cholinergic transmission and sphincter contractions on smooth muscle (Furness, 2000; Janig, 2006). The size and quality of the intestinal mucus layer is believed to be mediated by sympathetic innervation where mucosal immune system modulation (Elenkov et al., 2000) and microbial composition and behavior alterations (commensal and pathogenic) were seen (Macfarlane and Dillon, 2007; Rhee et al., 2009)

The Vagus Nerve and Beyond

The vagus nerve is the 10th cranial nerve and the fastest and most direct route that connects the gut and the brain. Its name is derived from the Latin for wandering, due to its extensive innervation, which allows collection of information from different visceral organs (Berthoud and Neuhuber, 2000). It is composed of 80% afferent and 20% efferent fibers (Agostoni et al., 1957; Prechtl and Powley, 1990), which tonically transmit vital information from the GI, respiratory and cardiovascular systems (bottom-up), and provide feedback to the viscera (top-down).

The gut is innervated by the hepatic and celiac branches of the vagus nerve, with decreasing density moving caudally from the proximal duodenum, ileum and the ileocecal junction as well as the remainder of the small and large intestines up to the level of the transverse colon (Wang and Powley, 2007). Vagal afferents form three different types of connections in the gut: Intraganglionic laminar endings and intramuscular arrays, which both end in muscle wall, as well as terminal axonal endings in the mucosa, and a recently described connection with a subset of enteroendocrine cells, now referred to as neuropods, which form synapses with vagal neurons (Kaelberer et al., 2018). Depending on their location and type, vagal afferents are ideally suited to detect stretch, tension or intestinal molecules such as bacterial by-products, gut hormones or neurotrans-

mitters. Due to the vast variety of receptors expressed on vagal afferents, they are thought to be polymodal, in that they respond to a variety of signals which are mechanical, chemical or hormonal in nature (Berthoud et al., 2004). Nevertheless, evidence suggests that there are distinct populations and subpopulations of vagal afferents responding to specific stimuli, including stretch (Williams et al., 2016a) or gut hormones (Egerod et al., 2018).

The vago-vagal anti-inflammatory reflex loop comprises vagal efferents originating mostly in the medullary dorsal motor nucleus of the vagus, which can modulate circulating levels of proinflammatory cytokines. Stimulation of the reflex can result in vagal modification of macrophage activation (Pavlov and Tracey, 2005), which is an important and well-documented mechanism involved in the pathophysiology of inflammatory bowel diseases (Mulak and Bonaz, 2004) (see **Section VIII.M**.). A reduction in parasympathetically controlled intestinal transit has been associated with an increase in small intestinal bacterial overgrowth and bacterial translocation (Van Felius et al., 2003). Moreover, pain responses in functional bowel disorders of the gut-brain axis such as IBS are associated with altered parasympathetic activity (Chey et al., 2001). Further, a biphasic vagal activation consisting of gastro-vagal inhibition and sacral activation has been correlated with the incidence of acute stress (Martinez et al., 1997) which potentially could lead to altered regional regulation of the microbiota.

Sensory vagal fiber cell bodies reside in the nodose ganglia and synapse on various nuclei of the brainstem. Vagal fibers from the GI tract mostly synapse bilaterally on the NTS; whereas afferents from the intestine synapse within the subnucleus commisuralis and medialis in the intermediate to caudal part of the NTS (Altschuler et al., 1993). From there Information is relayed to other brainstem nuclei and forebrain structures (Rinaman, 2010). Also, multisynaptic pathways ascending from the NTS link information from the viscera with the entire brain. Most of the sensory vagal afferents are glutamatergic, where second-order NTS neurons express α-amino-3-hydroxy-5-methylisoxazole-4-propionate (AMPA), N-methyl-D-aspartate (NMDA) and metabotropic glutamate (mGlu) receptors (Ambalavanar et al., 1998). In addition, NTS neurons express a variety of neuropeptides including cholecystokinin (CCK), prolactin-releasing peptide or pro-opiomelanocortin (Roman et al., 2016), and their receptors. Expression patterns of these neuropeptides and the target region of the axons can be used to sub-categorize NTS neurons, allowing the identification of NTS neurons responsible for specific emotional and behavioral responses (Maniscalco and Rinaman, 2018). For example, activation of projections of CCK and immunopositive neurons to the parabrachial nucleus results in decreased food intake without influencing anxiety-related behavior (Roman et al., 2016). In contrast, projections to the lateral hypothalamic area induce feeding behavior upon activation and projections from the NTS to the bed nucleus of the stria terminalis, and the central amygdala are involved in anxiety as well as fear and avoidance behaviors, respectively (Bienkowski and Rinaman, 2013). Furthermore, neuronal projections to the nucleus accumbens and the basolateral amygdala are capable of modulating memory facilitation after physiological arousal (Kerfoot et al., 2008; Roozendaal et al., 1999). By either direct or multisynaptic projections, the NTS is capable of influencing major neurotransmitter systems such as noradrenaline (A2 cell group in the NTS and locus coeruleus), dorsal amygdala (nucleus accumbens, ventral tegmental area) and 5-HT (dorsal raphe). It appears that the NTS is well suited to coordinate the integration of interoceptive feedback transmitted via the vagus nerve from the gut to the brain and from the brain to the periphery, thereby acting as an excellent

hub for microbiota-gut-brain signaling.

Studies utilizing vagotomy have clearly demonstrated the importance of constant bidirectional vagal signaling for appropriate brain function including host behavior. In humans, there have been older reports that ablation of the vagus nerve, a facet of gastrectomy formerly used for the treatment of peptic ulcer, resulted in an increase in the incidence of psychiatric-related disorders (Browning and Houseworth, 1953; Whitlock, 1961). Moreover, neurogenic bowel dysfunction is quite common in patients with chronic traumatic complete spinal cord injury (Zhang et al., 2018). In rodents, vagotomy results in decreased locomotor activity during the dark phase (Itoh et al., 1981) and increased epinephrine concentrations in plasma at baseline and after immobilization stress (Khasar et al., 2003; Mravec et al., 2015). Furthermore, vagotomy reduced proliferation and survival of newborn cells, decreased the number of immature neurons (O'Leary et al., 2018) and activation of microglia in the dentate gyrus (DG) of the hippocampus (Ronchi et al., 2012), all symptoms that can also be found in psychiatric disease (**Section VIII**). In addition, subdiaphragmatic vagal deafferentation (Vazquez et al., 2016) a method that eliminates abdominal vagal afferents, but keeps most efferents intact (Norgren and Smith, 1994) highlights the involvement of vagal afferents in anxiety-like (elevated plus maze, open-field test, food neophobia) and fear-related behavior (auditory-cued fear conditioning) (Klarer et al., 2014). Further, it demonstrated an enhancement in reinforced left-right discrimination and reversal learning (Klarer et al., 2017), sensorimotor gating (pre-pulse inhibition) and attentional control of associative learning such as conditioned taste aversion (Klarer et al., 2018).

Consistent with the data collected on vagotomy, studies on vagus nerve stimulation (VNS) support the role of the vagus nerve in mood regulation. In humans, VNS is used for the treatment of refractory depression (Breit et al., 2018) in addition to chronic pain (Chakravarthy et al., 2015; Ren et al., 1989) Crohn's disease (Bonaz et al., 2016), and certain epilepsies (Krahl, 2012; Penry and Dean, 1990). VNS in rodent models has shown to increase adult hippocampal neurogenesis (Grimonprez et al., 2015), and modulate the release of norepinephrine, 5-HT and dopamine in brain regions related to anxiety and depression (Breit et al., 2018), as well as increase hippocampal BDNF expression improving depressive-like behaviors in chronic restraint stress animals (Shin et al., 2019). Furthermore, a recent study in mice has shown that activation of GI vagal afferents influence reward behavior in mice (Han et al., 2018), further reinforcing the concept that vagal signaling is involved in behavior.

Evidence that gut bacteria utilize vagal afferents to alter their hosts' emotional and behavioral responses comes from studies observing changes in c-Fos expression in the cell bodies of vagal afferents following oral administration of *Campylobacter jejuni* (Goehler et al., 2005). *Campylobacter jejuni* administration had previously been shown to induce anxiety-related behavior without initiating a systemic immune response (Lyte et al., 1998). Moreover, vagotomy inhibited the effects of the prebiotic 2'-Fucosyllactose in associative learning related paradigms and hippocampal LTP (Vazquez et al., 2016). Interestingly, animals subjected to subdiaphragmatic vagal deafferentation show altered gene expression in the nucleus accumbens (Klarer et al., 2018). Further, an increase in the concentration of indole in the gut, a microbial metabolite, has been linked to the activation of the vagus nerve (Jaglin et al., 2018), similar to findings which show that administra-

tion of *L. rhamnosus* increases the firing rate of the mesenteric nerve bundle, which contains vagal and spinal afferents (Perez-Burgos et al., 2013)Cellular</keyword><keyword>Mice</keyword><keyword>*Neural Conduction</keyword><keyword>Pressure</keyword><keyword>*Probiotics</keyword><keyword>Reaction Time</keyword><keyword>Time Factors</keyword><keyword>Vagotomy</keyword><keyword>Vagus Nerve/*physiology/surgery</keyword></keywords><dates><year>2013</year><pub-dates><date>Jan 15</date></pub-dates></dates><isbn>1522-1547 (Electronic. Finally, recent studies in a genetic mouse model of autism (*Shank3B*$^{-/-}$ mouse) shows that the effects of *L. reuetri* on social behavior are no longer present in vagotomized animals (Sgritta et al., 2019). Despite plenty of evidence implicating the vagus as a conduit for microbiome to brain signaling, it has thus far not been possible to map the neuronal networks underlying microbiota-gut-brain axis in detail, and more work will be required to disentangle such circuits.

B. Enteric Nervous System (ENS)

At the interface between the microbiota and the host lies a network of neurons known as the enteric nervous system (ENS), positioned to respond either directly, or indirectly, to the microbiota and its metabolites. Broadly, the ENS is structured into two ganglionated plexi, the submucosal and myenteric plexus, and is largely responsible for the coordination of gut functions such as motility and control of fluid movement (Furness, 2012). In the context of gut-brain signaling, the ENS communicates with the CNS via intestinofugal neurons to sympathetic ganglia with sensory information traveling via extrinsic primary afferent neurons that follow spinal and vagal afferent routes (Furness, 2012). These intrinsic and afferent neural pathways provide opportunities for factors derived from the gut lumen, and therefore potentially the microbiota, to influence not only gut function but also the CNS.

ENS structure and neurochemistry resembles that of the CNS, and therefore any mechanisms implicated in CNS dysfunction may also lead to ENS dysfunction (Rao and Gershon, 2016) or *vice versa*. While the development of the ENS occurs primarily during embryogenesis, key events such as proliferation of progenitor cells, differentiation of mature neuronal phenotypes and formation of functional neural circuits continue during the postnatal period (Goldstein et al., 2013a), concurrent with the development of the gut microbiota (Wopereis et al., 2014). For example, the density of ganglion cells decreases significantly across the first 3 to 4 years of life (Burns and Thapar, 2013). This provides a critical window for the microbiota to influence the ENS during critical neurodevelopmental periods. We have recently reviewed the mechanisms by which the microbiota influences ENS development and function which includes activation of pattern recognition receptors including Toll-like receptors (TLR), in particular, TLR2 and TLR4, which are involved in recognition of microbial molecules (Hyland and Cryan, 2016). Inferences on the role of the microbiota on ENS development can also be drawn from studies in GF rodents (Hyland and Cryan, 2016; Kabouridis and Pachnis, 2015) (see **Table 2**).

Regarding the expression of pattern recognition receptors, the ENS has the molecular machinery to respond to viral RNA and LPS (the membrane component of gram-negative bacteria) (Raio and Phelps, 2015), through expression of TLRs 3,7 and 4 respectively (Barajon et al., 2009). Though an interesting observation, whether microbial factors can directly access the ENS, at least in a healthy state, remains unclear. Nonetheless, func-

tionally, the absence of TLRs impacts functions dependent on the ENS. For example, TLR4 deficient mice display a decrease in fecal pellet output and stool water content, perhaps reflective of alterations in myenteric and submucosal plexus function, respectively (Caputi et al., 2017), while TLR2 deficient mice display dysregulated small intestinal motility (Brun et al., 2015). A consistent finding across studies investigating members of the TLR family and the ENS have identified ultrastructural and neurochemical, as well as functional alterations between mice lacking TLRs, and their wild-type counterparts (Hyland and Cryan, 2016). Perhaps providing a more definitive role for the microbiota in this regard, GF mice also display significant ENS abnormalities in terms of ultrastructure and neurochemistry in the early postnatal period (Collins et al., 2014). These abnormalities observed in GF mice were not apparent in colonized animals, or following colonization with a defined bacterial consortia (ASF). This suggests that there is potential for particular bacterial species to play a role in determining the fate of ENS development and hints at the possible therapeutic application to offset detrimental factors which may negatively influence the trajectory of normal ENS development and function. In addition, GF animals also appear to display deficits in intrinsic sensory signaling, which one could infer might also consequently influence communication with the CNS. Moreover, this could be reversed upon conventionalization of the animals with microbiota from specific pathogen-free (SPF) donors (McVey Neufeld et al., 2015).

A recent study has provided mechanistic insight into how the microbiota might influence the ENS, implicating a role for 5-HT in this regard (De Vadder et al., 2018). Colonization of GF mice increased enteric neural 5-HT and expression of 5-HT_4 receptors while colonization of GF mice lacking tryptophan hydroxylase 1 (TPH1) failed to restore enteric neuron numbers to those observed in GF and conventional Tph1 transgenic mice and decreased Nestin+ neural precursors indicating reduced levels of neurogenesis (De Vadder et al., 2018). Moreover, colonization of GF mice in the presence of a 5-HT_4 receptor antagonist negatively influenced the ENS. In contrast stimulation of 5-HT_4 receptors in GF animals had the opposite effect and restored normal gut physiology (De Vadder et al., 2018). This work provides a body of evidence implicating a role for microbiota-induced effects on 5-HT and its impact on the ENS, though there are subtleties in the findings that would suggest this pathway may differentially influence neurogenesis, differentiation, cell turnover and gut function depending on the nature and timing of the interventions (Fig. 4.).

Antibiotic-induced disruption of the gut microbiota has also been applied as a method to determine the impact of this microbial community on the ENS and resulted in wide-ranging effects on ENS architecture (neuronal and glial), neurochemistry and function (Caputi et al., 2017) (see **Table 3**). Within enteric ganglia reside glial cells, which in antibiotic-treated animals were decreased (Caputi et al., 2017), and evidence from GF animals suggests a more specific role for the microbiota in modulating mucosal enteric glial cell migration which was not restricted to the early postnatal developmental period (Kabouridis et al., 2015). Notably, the density and proportion of Substance P-containing neurons, a neurotransmitter involved in motor and sensory neurotransmission in the gut, were increased in response to antibiotic-induced disruption of the gut microbiota as was the density of TLR2, which when activated partially recovered deficits in gut function (Caputi et al., 2017). These changes occurred concomitantly with a rebalancing of fecal bile acid profile reflected as increased levels of fecal taurocholic acid and a reduction of cholic acid in antibiotic-treated animals (Caputi et al., 2017). However, whether such changes in bile acid profile are mechanistically linked to the structural

and functional alterations in the ENS warrants further investigation. Notwithstanding this, in a mouse model of autism, not only was abnormal gut function observed, characterized by a constipation-like phenotype, ultrastructural and neurochemical changes in the ENS but also changes in fecal bile acid profile not dissimilar to those observed in antibiotic-treated mice, with elevated fecal taurocholic acid also observed in this mouse model of autism (Golubeva et al., 2017). However, shifts in the microbiota composition associated with stress and ENS abnormalities can occur independently of each other as observed in offspring of dams exposed to prenatal stress in which the most significant stress-induced changes in the gut microbiota failed to correlate with gut physiological and ENS parameters (Golubeva et al., 2015). Therefore, one must exert a degree of caution in interpreting concomitant changes in the microbiota and ENS as being intrinsically linked.

Microbial status, however, is not the only determinant of ENS function/ activity, which also displays sensitivity to exposure to early-life stress (De Palma et al., 2015). In a recent study, stress-induced alterations in ENS activity, characterized by stimulated acetylcholine release, was influenced by both maternal separation and the microbiota (De Palma et al., 2015), thus providing evidence that the microbiota may underpin ENS-related gut dysfunction associated with early-life stress. At a single cell level, GF status is accompanied by significant alterations in the electrophysiology and characteristic profile of after-hyperpolarization-type enteric neurons (intrinsic primary afferent neurons) reflected as decreased excitability and discharge (McVey Neufeld et al., 2013), which in the context of the microbiota-gut-brain axis may be especially important as these intrinsic afferent neurons may represent the first neural elements to sense changes in the microbiota with consequential effects on the gut and the brain. However, these single cell changes may not necessarily manifest as changes in gut function, where secretomotor responses, and those stimulated by capsaicin, and presumably driven by the submucosal plexus, were comparable in colonic segments from GF animals and colonized controls (Lomasney et al., 2014b).

In addition to displaying sensitivity to colonization with complex or simplified microbiota, the ENS also responds to specific bacterial strains, or components thereof, perhaps providing some insight into the microbial mechanisms which may affect ENS function. While some of these studies have taken a direct approach by stimulating enteric neurons with bacterial supernatants or conditioned media (Khoshdel et al., 2013; Kunze et al., 2009), others have considered the epithelial barrier which separates the gut lumen from its underlying nervous system (Al-Nedawi et al., 2015; Kunze et al., 2009). The latter approach has demonstrated that not only do different bacterial strains differentially influence enteric nerve activity but that they may do so by different mechanisms (Mao et al., 2013). *Bacteroides (B.) fragilis* for example, likely as a consequence of its capsular exopolysaccharide, can influence ENS function while an *L. rhamnosus* strain (JB-1) does so via a G-protein-coupled receptor-mediated pathway (Mao et al., 2013). Of note in this latter study, the authors show that the effects on the ENS are not dependent on diffusion of molecules from the epithelium to the myenteric neurons. Using a similar methodology, the same laboratory also demonstrated that the microbial-derived SCFA, butyrate, and epithelial-applied 5-HT, could affect ENS activity providing some further insight into additional mechanisms by which the microbiota may interact with the ENS (Kunze et al., 2009). Functional studies support that different microbial strains can differentially affect neurally-driven secretomotor responses (Lomasney et al., 2014a). Further characterization of the mechanism underlying the effect of the *L. rhamnosus* strain (JB-1) on ENS function confirmed that an intact epithelium was required to mediate

the effect of microvesicles derived from JB-1, which themselves recapitulated the effects of the strain *per se* on the ENS (Al-Nedawi et al., 2015), indicative that epithelial elements may be an important intermediary in transducing microbial signals from the gut lumen to the ENS. The ENS is also central to facilitating changes in motility consequential to diet-microbe interactions (Dey et al., 2015).

Evidence now also suggests that there may be a reciprocal relationship between the ENS and the gut microbiota. Thus far, we have considered the impact of the microbiota on the ENS. However, the ENS appears to be able to exert control of the microbiota (Rolig et al., 2017). In zebrafish lacking an ENS as a consequence of a mutation in an SRY-related HMG-box (*sox10* transcription factor gene), a 'pro-inflammatory' microbiota profile developed, the effects of which could be ameliorated by transplantation of wild-type ENS precursors into *sox10* mutants or by the introduction of 'anti-inflammatory' microbes (Rolig et al., 2017). These data might challenge the dogma that alterations in the microbiota precede alterations in the ENS and thus lead to the proposal that changes in neural activity may precede alterations in the gut microbiota.

Abnormalities in the ENS are associated with life-threatening GI disorders including, Hirschsprung disease and neuropathic chronic intestinal pseudo-obstruction (Gariepy, 2001). Also, the ENS has now also been implicated in disorders of the CNS, including ASD, Alzheimer's disease and Parkinson's disease, generally considered primary disorders of the CNS (Rao and Gershon, 2016). ASD is particularly noteworthy given the high level of comorbid GI symptoms observed (Rao and Gershon, 2016) (see **Section VIII. A.**). Future studies are needed to fully appreciate the relative contribution of the microbiota in shaping the pathological effects of ENS dysfunction.

C. Immune System and Neuroimmunity

The GI tract harbors the densest concentration of immune cells in the body and is in constant communication with the trillions of microbes that inhabit our gut, either through direct physical contact or the release of secreted compounds (**Fig. 4.).** As such, one critical function of the single-cell layer of our gut is to limit the contact of intestinal microbiota with the visceral tissue, which it does by secreting a protective viscous mucus layer from goblet cells of the epithelium. This luminal-mucosal interface is where the majority of host-microbe interaction occurs, and the exchange of molecules through the mucous layer and epithelium serve to facilitate communication between the gut and the immune system through the recognition of self and non-self antigens (Fasano and Shea-Donohue, 2005), and thus to prime the immune system to identify potentially harmful pathogens.

As well as providing a physical barrier, the epithelium contains a number of different cell types including enterocytes, secretory cells, chemosensory cells and gut-associated lymphoid tissue (Pott and Hornef, 2012). The enterocytes express innate immune receptors and can release cytokines and chemokines, while the gut-associated lymphoid tissue utilizes lymphocytes to mount a more specific immune response (immunoglobulins). Chemosensory cells play a key role in defense against helminths (Allaire et al., 2018), while secretory cells are involved in mucus release from goblet cells, the release of antimicrobials from Paneth cells and

the release of neuroendocrine compounds including ghrelin, somatostatin, cholecystokinin, peptide YY and 5-HT amongst others from enteroendocrine cells (Cani et al., 2013).

Peptidoglycans, polysaccharides and other antigens on bacteria that confer beneficial roles for the bacteria (protection against degradation) also allows the host immune cells to identify the numerous and diverse bacteria to the host, and to identify a change in the homeostatic balance of the gut. Epithelial pattern recognition receptors recognize molecular patterns unique to bacteria and other microorganisms (pathogen-associated molecular patterns) (Duerkop et al., 2009; Vaishnava et al., 2008) of which the TLR family are the most studied, and once activated can recruit inflammatory mediators, cytokine production and chemokine-mediated recruitment of acute inflammatory cells (Takeda and Akira, 2004).

Along with activating the innate immune system, many commensal bacteria metabolites including neuromodulators, bacteriocins, bile acids, choline and SCFA's are immunomodulatory (**Fig. 4.).** A growing body of evidence suggests that microbiota-host interactions at the level of the gut leads to the release of cytokines, chemokines, neurotransmitters, neuropeptides, endocrine messengers and microbial by-products that can infiltrate the blood and lymphatic systems, or influence neural messages carried by the vagal and spinal afferent neurons to constantly communicate with the brain and update as to health status, and possibly to regulate brain and behavior. However, it seems unlikely that any one of these classes of compounds is individually responsible for mediating all microbiota-gut-brain interactions and these will be discussed individually in subsequent sections.

Innate Immune System

The immune system is subdivided into two separate subsystems –innate and adaptive/ acquired. Innate immunity is regarded as the body's primary line of defense against potentially infectious organisms and involves the activity of cells derived from the myeloid lineage – monocytes and macrophages, basophils, eosinophils, and neutrophils, in addition to mast cells, platelets, and natural killer cells (Stewart, 2012). The gut microbiota influences the relative populations, migration, and function of various subsets of immune cells including Helper T cells, Regulatory T cells, mononuclear phagocytes and innate lymphoid cells (Dorrestein et al., 2014; Rooks and Garrett, 2016), and the mechanisms as to how a microbial population of the gut can modulate both the innate and adaptive immune responses at mucosal surfaces during infection, inflammation, stress, and autoimmunity are being unraveled (Cassel et al., 2008; El Aidy et al., 2015; Kamada et al., 2013a; Mazmanian et al., 2005; Powell et al., 2017). However, until recently, the interaction between microbes confined to the gut and immune cells of the brain had not been investigated.

As alluded to in earlier sections microbiota-microglia interactions are receiving much attention of late as key mechanisms underlying microbiota-immune-brain interactions (Abdel-Haq et al., 2019; Rea et al., 2016; Vuong et al., 2017). The CNS-restricted microglia are innate sentinel immune cells that can detect subtle changes in the surrounding molecular milieu (Bilbo and Schwarz, 2012; Delpech et al., 2015; Hickman et al., 2013; Kim and de Vellis, 2005; Nimmerjahn et al., 2005; Tremblay et al., 2011), and are responsible for

the mounting of neuroinflammatory responses (Kettenmann et al., 2011; Ransohoff and El Khoury, 2015; Yamasaki et al., 2014). These resident cells compromising 5-12% of all cells in the brain are highly ramified and extremely plastic, and once activated can release a number of cytokines and chemokines, express numerous antigenic markers, regulate neurotransmitters and undergo extreme morphological changes (Pocock and Kettenmann, 2007). Cytokines and chemokines are chemical messengers involved in recruiting other immune cells to the vicinity, the repair of damaged tissue and the restoration of homeostasis (Charo and Ransohoff, 2006). Cytokines are generally classed as pro-inflammatory or anti-inflammatory, which facilitate or inhibit inflammatory processes respectively, and both play an equally important role in the mounting of a suitable physiological neuroinflammatory response, and the return to homeostasis. Indeed, the balance between these anti- and pro-inflammatory cytokines and chemical messengers are key determinants in an appropriate defense of the host against infection or tissue damage.

Along with their established immune role in the CNS, the constitutively active microglia are critically involved in neuronal events at various stages in development and adulthood, including synaptic remodeling to improve neuronal network signaling (Schafer and Stevens, 2015). Recently, it was determined that a diverse GI microbiota is necessary for the maintenance of, and maturation of, microglia in a healthy functional state (Erny et al., 2015). In contrast, the absence of a complex host microbiota (when using GF animals or antibiotic-treated mice) increased microglial populations, caused defects in microglia maturation, activation state and differentiation, altered microglia morphology (with longer processes and increased branching, terminal points and clubbing at synaptic boutons), and compromised immune response to bacterial or viral infection (Erny et al., 2015). These alterations in microglial phenotype were reversed with recolonization of gut microbiota, following six weeks co-habitation of GF mice with control mice. These findings demonstrate that a healthy and diverse GI microbiota is essential for the continuous preservation of healthy microglia and proper brain function throughout our lifespans (Cryan and Dinan, 2015a; Thion et al., 2018).

Aside from releasing cytokines and chemokines to recruit local immune cells, microglia also recruit monocytes from the periphery to the brain to aid in defense and cell debris clearing. While the multimodal influence of microbiota on physiological events at the level of the CNS has gained credence, more recently there has been a shift toward understanding the role of the microbiota in regulating neuroinflammation via intervention in the recruitment of local immune regulators (trafficking monocytes) from the periphery to the brain (Wohleb et al., 2014). Evidence suggests that the trafficking of these monocytes to the brain appeared to be governed by TNFα-mediated microglia activation (D'Mello et al., 2009) and was reversible in preclinical studies with probiotic intervention with VSL#3 (D'Mello et al., 2015). Indeed, the mediation of certain behavioral phenotypes as a consequence of prolonged HPA axis activation involves the trafficking of monocyte from the spleen (Wohleb et al., 2014), a tissue with a high density of free fatty acid receptor type 2 (FFAR2) (Erny et al., 2015). These FFAR2 receptors are G-protein coupled receptors that have been localized to peripheral lymphocytes (Nilsson et al., 2003)FFA2R, expressed on leukocytes and activated by short-chain fatty acids</title><secondary-title>Biochem Biophys Res Commun</secondary-title></titles><pages>1047-52</pages><volume>303</volume><number>4</number><edition>2003/04/10</edition><keywords><keyword>Amino Acid Sequence</keyword><keyword>Animals</keyword><keyword>Calcium/metabolism</keyword><keyword>Dose-Response Relationship, Drug</keyword><keyword>Fatty Acids, Volatile/*phar-

macology</keyword><keyword>Humans</keyword><keyword>Leukocytes/*metabolism</keyword><keyword>Ligands</keyword><keyword>Mice</keyword><keyword>Molecular Sequence Data</keyword><keyword>RNA, Messenger/biosynthesis</keyword><keyword>Rats</keyword><keyword>Receptors, Cell Surface/genetics/*metabolism</keyword><keyword>Sequence Homology, Amino Acid</keyword><keyword>Tissue Distribution</keyword></keywords><dates><year>2003</year><pub-dates><date>Apr 18</date></pub-dates></dates><isbn>0006-291X (Print. GI microbiota are responsible for the production of SCFAs, the natural ligands for FFARs, which were shown to reverse the detrimental effects on microglia density, morphology, and maturity in the absence of a complex microbiota (Erny et al., 2015). Taken together these findings suggest that GI microbiota may govern centrally mediated events indirectly through regulation of monocyte trafficking to the brain and subsequent microglia activation, possibly via SCFA-mediated mechanisms.

Adaptive Immune System

Adaptive immunity induces a specifically targeted response to pathogens and is comprised of cells originating in the lymphoid lineage (i.e. B and T lymphocytes). The adaptive immune system distinguishes itself by its specialization, specificity, memory, regulation, diversity and tolerance (Vanguri, 2014). Furthermore, these cells are also capable of secreting both pro- and anti-inflammatory (Chung, 2009). The adaptive immune system develops postnatally and is, therefore, critically shaped by exposure to microbes. Further, disease states such as allergy and asthma and/or the immune hypothesis of depression/schizophrenia, are linked to the disruption of microbes and immune function.

Over the last decade, efforts have been made to increase our understanding of the potential role the adaptive immune system plays in the brain and behavior (Amor and Woodroofe, 2014; Filiano et al., 2015; Monteiro et al., 2016). Recent intriguing studies in recombination activation gene 2 knockout (Rag2) transgenic mice, which lack mature B and T lymphocytes , showed that adoptive transfer of lymphocytes from stressed mice reduced anxiety, increased social behavior, and increased hippocampal cell proliferation compared with those receiving no cells or cells from unstressed donors (Brachman et al., 2015), and that transferred lymphoid cells infiltrate the choroid plexus and the meninges (Scheinert et al., 2016). Recently, intraepithelial lymphocytes (CD4CD8αα+ double-positive T cells specifically) were shown to require the presence of *L. reuteri,* in combination with a tryptophan-rich diet, to reprogram intraepithelial CD4+ T cells into immunoregulatory T cells (Cervantes-Barragan et al., 2017), evidence that gut microbiome influences/interacts with the adaptive immune system. Further, *Drosophila* social behavior appears to be regulated through immunoregulation and microbiota maintenance (Chen et al., 2019). This finding reveals that adaptive immune cells might be mediating the behavioral response to stress thus representing an interesting novel pathway, which needs to be further explored.

Interestingly, adaptive immunity and the intestinal microbiota also seem to be acting synergistically towards modulating homeostasis. IgA plasma cells from the gut are able to access the CNS in the induction of experimental autoimmune encephalomyelitis multiple sclerosis mouse model, and that these cells suppress inflammation in a pathway that involves IL-10 (Rojas et al., 2019). In Rag2 transgenic mice, adaptive immunity

influences microbiota composition (Galvez et al., 2017). A link between stress, the microbiota, and the adaptive immune system has been illustrated in a recent study examining the impact of chronic stress on long-lasting altered levels of IL-10+ T regulatory cells (Bharwani et al., 2016). The expression of IL-10 was associated with an increased abundance of *Clostridium*, therefore reinforcing the hypothesis that microbes in the gut, the adaptive immune system, and the central nervous system may be working synergistically. Subsequently, it was shown that the impairment in the adaptive immune system in Rag1 transgenic mice is linked to alterations in cognition and anxiety-like behavioral tasks, which were ameliorated by treatment with a combination of *L. rhamnosus* and *L. helveticus.* This study, therefore, establishes that lymphocyte deficiency results in impairments in behavior, which can be normalized by probiotic treatment, implicating a specific role of adaptive immunity in the microbiota-gut-brain axis (Smith et al., 2014). Adaptive immunity has also been shown to respond to specific bacterial antigens which are modulated by dietary components, suggesting that dietary modifications could be a therapeutic avenue for human disease such as IBD (Wegorzewska et al., 2019). A link between the adaptive immune system, IFNy signaling in the meninges, and social behavior was also illustrated (Filiano et al., 2016). This study showed how IFNy acts as a link between meningeal immunity and neural circuits recruited for social behavior. Given the importance of the microbiome in shaping social behavior (see **Section X.B**) further studies should focus on the possible role of the microbiome in shaping such immune-brain communication.

K. Enteroendocrine Signaling

Though enteroendocrine cells (EECs) represent only 1% of epithelial cells in the GI tract, they are critically important for the maintenance of gut homeostasis due to the pleiotropic effects of their secreted signaling molecules. Ten different types of EECs have been described so far, all of which are sensory cells, coordinating changes in the gut-nutrient luminal content with metabolic and behavioral responses, such as the regulation of insulin secretion or food intake (Gribble and Reimann, 2016). Two of the best understood EEC's are enteroendocrine L cells and enterochromaffin cells which are abundant in the distal small and large intestines, where the majority of bacterial taxa reside. They can establish direct contact with the luminal constituents via the apical surface, including bacterial metabolites. They have a long lifespan (Bohorquez et al., 2015; Tsubouchi and Leblond, 1979), potentially enabling them to integrate into the local signaling network of the enteric nervous system, glia and immune cells of the GI submucosa.

Enteroendocrine L cells

Enteroendocrine L cells secrete glucagon-like peptide-1 (GLP-1) and peptide YY (PYY) in the postprandial state. Both peptides are potent anorexigenic hormones involved in the modulation of eating. The receptors to these peptides are expressed locally in the gut enteric neurons and vagal afferents, as well as in the central nervous system (CNS), including the brainstem and hypothalamus (De Silva and Bloom, 2012; Richards et al., 2014). GLP-1 and PYY can stimulate satiation and inhibit eating, acting either directly on the hypothalamic centers of appetite control, or indirectly via the vagal-brainstem-hypothalamic pathway (Latorre et al., 2016; Steinert et al., 2017). Which of these pathways is more important for the effects of peripherally released hormones on food intake is still not fully understood. Notably, a new route of communication between L

cells and the enteric nervous system has recently been discovered (Bohorquez et al., 2014; Bohorquez et al., 2015; Kaelberer et al., 2018). A basolateral cytoplasmic process of the L cells – the neuropod – was shown to establish a functional synaptic contact with the enteric glia and vagal afferents. The existence of synaptic connections between L cells and the ENS suggests that the EECs signaling from the gut to the brain can respond more precisely and much faster than we initially thought and that the CNS can have a tuning effect on the L cells.

In the proximal gut, the release of GLP-1 and PYY is activated mainly by luminal nutrients, providing a postprandial spike of peptide release. For instance, L cells can sense carbohydrates via the sodium-coupled glucose transporter (SLC5A1) (Gorboulev et al., 2012; Reimann et al., 2008), long-chain fatty acids via FFAR1 and FFAR4 receptors (Edfalk et al., 2008; Hirasawa et al., 2004), and monoacylglycerols via the GPR119 receptor (Reimann et al., 2008). Strikingly, in the distal gut, the activation of L cells is triggered almost exclusively by bacteria-derived metabolites. Moreover, SCFAs can stimulate the secretion of GLP-1 and PYY through the FFAR2 and, to a lesser extent, the FFAR3 receptor (Lin et al., 2012; Psichas et al., 2015; Tolhurst et al., 2012). Bacteria-derived secondary bile acids (lithocholic acid, deoxycholic acid) can activate the G-protein coupled bile acid receptor Gpbar1 receptor (TGR5) in L cells, promoting the peripheral release of GLP-1 and PYY (Katsuma et al., 2005; Thomas et al., 2009; Ullmer et al., 2013). Indole was shown to induce GLP-1 secretion (Chimerel et al., 2014). Further, bacterial LPS were recently shown to enhance GLP-1 secretion, suggesting the involvement of TLR's in L cell activity (Larraufie et al., 2017; Nguyen et al., 2014).

Because bacterial fermentation of non-digested nutrients continues between meals, bacterial metabolites can support the activity of colonic L cells and the secretion of anorexigenic hormones for many hours after a meal (Gribble and Reimann, 2016). This basal secretion of GLP-1 and PYY is thought to play an important role in the control of food intake, body weight, and metabolism since obese individuals are generally characterized by decreased serum levels of both GLP-1 and PYY (De Silva and Bloom, 2012). Changing the fermentation capacity of the gut microbiota through chronic dietary supplementation of prebiotics or probiotics was quite successful in decreasing food intake, body weight and improving glucose tolerance in preclinical models of obesity and diabetes (see **Tables 4, 5**; for further details, see review (Plovier and Cani, 2017)). Some prebiotics, a polysaccharide inulin as well as FOS and GOS were shown to increase the production of both GLP-1 and PYY (Cani et al., 2005; Everard et al., 2011). Certain *Lactobacillus* strains were capable of stimulating GLP-1 production both *in vitro* and *in vivo* (Balakumar et al., 2018; Panwar et al., 2016; Simon et al., 2015). Altogether, these findings clearly demonstrate the importance of bacterial metabolites and adequate diet in the maintenance of metabolic health, and that gut microbes can regulate the secretion of GLP-1 and PYY.

Although EEC L cells are perhaps the best-studied component of the host-microbe dialogue at the enteroendocrine interface other protagonists have also emerged. Autoantibodies directed against the peptide α-Melanocyte-stimulating hormone (α-MSH), which is involved in appetite control, have been discovered in both healthy individuals and in subjects with eating disorders (Fetissov et al., 2002; Fetissov et al., 2008). Many of these antibodies represented the IgA class, which points to an intestinal origin of such antigens. This was a genuinely intriguing discovery because it raised the possibility that across evolution, in close interactions with the host, bacterial taxa could have acquired protein mimetics of mammalian appetite-reg-

ulating hormones. This endows gut bacteria with a powerful tool to control nutrient supply by manipulating host food intake. A few years later a caseinolytic protease B (ClpB) heat-shock protein was discovered in gut commensal *E. coli,* an antigen-mimetic of α-MSH which confirmed this hypothesis (Tennoune et al., 2014). Moreover, it was shown that ClpB plasma levels were elevated in a variety of eating disorders, and its concentration has been correlated with various psychopathologic traits (Breton et al., 2016a). Moreover, chronic intragastric delivery of ClpB-expressing *E. coli* in mice stimulated the production of α-MSH-reactive antibodies and decreased food intake (Breton et al., 2016b; Tennoune et al., 2014). Interestingly, peripheral α-MSH was shown to trigger the release of PYY and GLP-1 from EEC L cells in the gut via activation of the melanocortin 4 receptor (Panaro et al., 2014). This suggests PYY and GLP-1 could mediate the effects of bacterial ClpB on satiety. These ground-breaking findings posit that evolution of molecular mimicry between gut bacteria and the host (Oldstone, 2005) can affect host eating behavior. Most intriguingly, humans seem to carry autoantibodies to some appetite-regulating peptides including PYY and ghrelin (Fetissov et al., 2008), and the corresponding bacterial antigens, as well as their physiological role, have yet to be unraveled.

Enterochromaffin Cells

Enterochromaffin cells (ECs) produce the majority of 5-HT in the body from dietary tryptophan (see also **Section VII E)**. 5-HT activates a diverse family of receptors on intrinsic and extrinsic afferent nerve fibers in the GI tract and mediates many GI functions including intestinal peristalsis, electrolyte secretion, pain perception and inflammatory responses (Mawe and Hoffman, 2013). Unlike L cells, interactions between gut microbiota and ECs are much less understood.

Taking advantage of GF mice, recent studies have shown that specific gut bacterial strains, such as the spore-forming clostridia taxa, can up-regulate the expression of colonic TPH1 (the rate-limiting enzyme in the production of 5-HT), boosting 5-HT biosynthesis in the gut, and increasing intestinal transit in the host (Reigstad et al., 2015; Yano et al., 2015). It is unclear whether this was a direct interaction of bacteria with ECs or indirect stimulation of ECs with bacterial metabolites. However, a single intrarectal injection of deoxycholic acid (a secondary bile acid produced by clostridia) could partially replicate the effects of the bacteria (Yano et al., 2015). Interestingly, earlier findings suggest that secondary bile acids can mediate the effect of gut bacteria on 5-HT synthesis in the host. ECs were shown to express TGR5, and administration of deoxycholic acid increased 5-HT secretion in colonic tissue of the wild-type, but not Tgr5 transgenic mice (Alemi et al., 2013). There is also evidence that bacterial LPS can increase 5-HT secretion via TLR4 activation in ECs isolated from Crohn's disease patients, but not from healthy subjects (Kidd et al., 2009).

Variations in intestinal 5-HT production are unlikely to have a direct effect on the brain because 5-HT cannot cross the BBB (Donovan and Tecott, 2013). The availability of tryptophan for the brain, as a source for 5-HT synthesis, is also partially determined by the metabolism of tryptophan along the physiologically dominant kynurenine pathway (Kennedy et al., 2017) (see **Section IV.E.**). However, by modulating vagal afferent activity (Mawe and Hoffman, 2013) and inflammatory responses in the gut (Shajib et al., 2017), 5-HT released from EC cells can potentially have an impact on gut-brain signaling. Perhaps the best-known example of such an interaction is during chemotherapy-induced nausea and emesis, caused by a massive release of intestinal 5-HT

and consequent activation of vagal afferents in the gut (Gale, 1995). More recently, altered 5-HT signaling has been associated with IBS (Mawe et al., 2006) (see **Section VIII.M.**). Moreover, in a mouse model of ASD (the BTBR *T*$^{+}$ *Itpr3*^{tf}/J mouse), (see **section VIII.A.**) (Kong et al.; Meyza et al., 2013; Moy et al., 2007), a strong association between the reduction in the relative abundance of *Blautia* species from *Clostridiales* order and a decrease in 5-HT production in the gut was observed (Golubeva et al., 2017). Further studies utilizing specific bacterial strains with pro-5-HT activity (such as bile-metabolizing clostridia) are required to shed more light on the role of gut microbiota and intestinal 5-HT in gut-brain communication.

Adding to the complexity of this task, it is worth noting that EC-produced 5-HT is not only secreted towards the intestinal submucosa, but a substantial amount of 5-HT is continuously released in the apical direction, which can be easily detected in the gut lumen (Patel, 2011). Furthermore, gut bacteria were shown to deconjugate host-produced catecholamines via the β-glucuronidase enzyme pathway, and thus generate free luminal 5-HT (Asano et al., 2012; Hata et al., 2017). The physiological consequences of these processes, either for the host or the microbiota, are not yet known or will be the subject of future studies.

L. Neurotransmitters

Microbial endocrinology is becoming an important concept in advancing our knowledge of the microbiota-gut-brain axis, helping move our understanding from correlation to causation (Lyte, 2014). One of the main facets of the concept of microbial endocrinology is based on the shared neurochemical language that exists between host and microbe. It has been long understood that microbes are capable of producing neurochemicals that we typically associate with mammalian organisms. Landmark studies in the 1990s were the first and demonstrate that bacteria respond to host neuroendocrine signaling molecules (Lyte and Ernst, 1992, 1993), including norepinephrine and epinephrine, and that the microbiota can affect host behavior via the gut-brain axis (Lyte et al., 1998). Since that time, the microbiota has been shown to synthesize and respond to several key neurochemicals (e.g. 5-HT, GABA, amongst others) that are involved in host mood, behavior, and cognition. Many of these host- and microbial-derived neuroactive molecules are also important signaling molecules in host-microbiota interactions at the intestinal interface.

Catecholamines

Catecholamines play diverse roles in host physiology, ranging from the stress-induced fight-or-flight response (Starkman et al., 1990) to influencing gut integrity (Meddings and Swain, 2000) and affecting host motivational behavior as well as decision-making (Terbeck et al., 2016). Likewise, norepinephrine and epinephrine induce wide-ranging responses in bacteria, including the promotion of pathogenesis and growth (Lyte et al., 2016). The catecholaminergic system was one of the first demonstrated to mediate host-microbe cross-talk, and holds important clinical implications for both animals and humans (Lyte, 1993). Although it was previously accepted that susceptibility to illness following acute stress was a consequence of a suppressed immune system, it was shown that the host production of norepinephrine caused the induction of bacterial virulence genes, thereby driving infection and mortality (Lyte, 2014). Norepinephrine signals these changes in bacteria via several methods, including possible receptor-based mechanisms. At increasing levels within the host,

norepinephrine exerts a chemotactic effect on bacteria, which can increase bacterial migration toward the host intestinal mucosa (Lyte et al., 2018). Second, catecholamines can behave as siderophores, which cause the release of iron from host-iron sequestering proteins, increasing the availability of iron for bacteria, thereby enhancing bacterial growth (Freestone et al., 2012). Also, norepinephrine can act as a quorum sensing molecule to increase the expression of bacterial virulence genes through interaction with bacterial quorum sensing histidine kinase (Curtis et al., 2014; Moreira et al., 2016). In GF rodents circulating norepinephrine concentration is higher compared to conventional rodents (Kingsley et al., 1991), and within ileal, cecal, and colonic lumens, dopamine, norepinephrine, and epinephrine are detectable (Asano et al., 2012).

Enteric nerves contain the requisite genetic machinery to synthesize dopamine and norepinephrine, but lack phenylethanolamine N-methyltransferase, the enzyme that converts norepinephrine into epinephrine (Costa et al., 2000). This is an important consideration because the microbiota, and in particular the bacterial enzyme β-glucuronidase, have been demonstrated to play a critical role in converting host norepinephrine and dopamine from a biologically-inactive to a biologically-active form (Asano et al., 2012). It was recently demonstrated that certain bacteria contain plasma membrane monoamine transporter and organic cation transporter proteins which enable the transfer of extracellular norepinephrine into the bacterial cell (Lyte and Brown, 2018).

A variety of bacteria, many of which are found within the human GI tract, are recognized to produce catecholamines that are identical in chemical structure to those produced by the host. Evolutionary adaptations, including late horizontal gene transfer (Iyer et al., 2004), have been proposed to explain bacterial metabolic pathways of neuroendocrine molecules. Briefly, members of the genus Escherichia, including human gut commensals, are known to produce catecholamines, such as norepinephrine (Shishov et al., 2009). Bacillus are likewise known to produce norepinephrine in addition to dopamine (Tsavkelova et al., 2000). Although several host cell types in the GI tract are responsive to catecholamines (Bellono et al., 2017), it is largely unknown how catecholamines of bacterial origin influence host physiology.

Gamma-amino-butyric acid (GABA)

Both host and bacteria have the capacity to convert the amino acid glutamate to GABA (Smith et al., 1992; Strandwitz et al., 2019), the major inhibitory neurotransmitter of the host nervous system. Indeed, *Escherichia spp.* (Richard and Foster, 2003) and *Lactobacillus spp*. (Siragusa et al., 2007) have been demonstrated to synthesize GABA. Additionally, several fermented foods used by *Lactobacillus* spp. also contain millimolar levels of GABA, such as the Chinese paocai (Li et al., 2008). Interestingly, certain *Lactobacillus spp*. identified in fermented foods are also known to synthesize glutamic acid (Zareian et al., 2012). Although the importance of the bacterial production of GABA in the host intestinal lumen is unclear, GF mice exhibit significantly lower luminal GABA levels compared to mice that have a microbiota (Matsumoto et al., 2012). Interestingly, it has been shown that the probiotic *E. coli* strain Nissle 1917 (EcN) can produce a GABA associated analgesic lipopeptide, C12AsnGABA OH (Perez-Berezo et al., 2017). They were able to demonstrate that the addition of the C12AsnGABA OH moiety to GABA facilitated diffusion across the epithelial barrier, allowing the activation of GABA receptors on sensory neurons. It is currently unknown if this is a common feature of other microorgan-

isms in the GI tract. In a study examining *Lactobacillus spp.* and *Bifidobacterium spp.* isolated from the human GI tract, five strains were found to convert GABA from monosodium glutamate (Barrett et al., 2012). Recently, evidence from the Human Microbiome Project has suggested the fecal microbiome contains the capacity to encode glutamate decarboxylase, the enzyme that converts glutamic acid to GABA (Pokusaeva et al., 2017). The oral administration of *B. dentium*, a GABA-producing bacterial species isolated from human feces, was shown to inhibit visceral hypersensitivity in rats suggesting functional insight into the *in vivo* function of bacterial-produced GABA (Pokusaeva et al., 2017). Likewise, bacteria express receptors capable of sensing extracellular, GABA (Guthrie and Nicholson-Guthrie, 1989). It is therefore likely that host production of GABA can influence the microbiota. Indeed the administration of GABA to *Pseudomonas aeruginosa* culture has been demonstrated to increase the organism's virulence (Dagorn et al., 2013). Further studies are required to reveal the functional dynamics and importance of glutamate and GABA as mediators of host-microbe crosstalk.

Histamine

Histamine is a biogenic amine that is synthesized from histidine via histidine decarboxylase. This enzymatic pathway is conserved among mammals and certain species of bacteria, and therefore represents an important area of host-microbe communication (Bailey et al., 2011). In mammals, histamine plays several roles in host physiology including modulating wakefulness (Thakkar, 2011) as well as a diverse array of immune functions. Several host immune cell-types synthesize histamine, including mast cells and gastric enterochromaffin-like cells (Andersson et al., 1998), which are found in the GI mucosa, are at the interface of host-microbe interaction. Mucosal mast cell degranulation within the gut can affect host intestinal integrity (Santos et al., 2001) and has been related to visceral pain (Barbara et al., 2004). The bacterial production of histamine has long been recognized as an important food safety concern (Colombo et al., 2018). Interestingly vagal afferents can respond to histamine (Keita and Soderholm, 2010), suggesting a route by which microbial-derived histamine may interact with the host nervous system. Although the microbiota contains bacterial species capable of synthesizing histamine, it is not yet clear how this influences host physiology. For example, commensals *Morganella morganii* and *E. coli*, have been shown to produce biogenic amines (Pugin et al., 2017), including histamine (Behling and Taylor, 1982; Kim et al., 2000). Indeed, the human fecal microbiota is enriched with bacterial species that express the histidine decarboxylase gene, suggesting a capacity to synthesize histamine within the host gut (Barcik et al., 2016). Although little is known about how the microbial production of histamine in the host gut affects host physiology, *in vitro* evidence has shown histamine produced by *L. reuteri* suppressed human monocytoid production of tumor necrosis factor (TNF)-α via the TLR (Thomas et al., 2012). Perhaps most interestingly, *L. reuteri* was shown to modulate host gut immune function (Ferstl et al., 2014), as well as intestinal inflammation via the histamine H2 receptor (Gao et al., 2015). It is clear that histamine functions as a neuroendocrine-immune mediator of host-microbe crosstalk; however, how host histamine may impact microbial function remains to be uncovered.

Serotonin, Tryptophan, and Kynurenine

Serotonin (5-HT) is a neurotransmitter produced from tryptophan via the enzyme tryptophan hydroxylase (TPH). The capacity to synthesize 5-HT from tryptophan is widely conserved among mammals and several bacterial species (Bailey et al., 2011). In mammals, 5-HT plays diverse roles ranging from modulation of host

behavior to impacting GI motility as well as influencing bone remodeling and erythrocyte health (Spohn and Mawe, 2017). Although enterochromaffin (EC) cells of the GI tract are responsible for over 95% of the body's 5-HT production (Foster et al., 2017), the gut microbiota are understood to impact the host GI serotonergic system (Hata et al., 2017; O'Mahony et al., 2015). Indeed, it has been long appreciated that the bacterial species *C. perfringens*, a member of the human and rodent microbiota, modulates gut production of 5-HT (Beaver and Wostmann, 1962). It was recently demonstrated that *C. perfringens* modulates host colonic 5-HT synthesis via host TPH-1 (Yano et al., 2015). Since microbial products such as SCFAs modulate host TPH-1 (Reigstad et al., 2015), there may be microbial regulation of host GI motility via the gut serotonergic system (Ge et al., 2018). Likewise, 5-HT concentrations in the cecal and colonic lumens are significantly reduced in GF mice (Hata et al., 2017). The conventionalization of GF mice with a microbiota resulted in increased concentrations of intestinal luminal 5-HT. Moreover, in the same study, the conjugated, biologically inactive form of 5-HT was found at a higher percentage in GF mice, whereas the unconjugated, biologically-active form of 5-HT was found in greater concentration in conventionalized GF mice. Indeed, transporter-based mechanisms for the update of extracellular 5-HT were recently highlighted in a probiotic strain of *Lactobacillus*. As a neuroendocrine signal of host-microbe crosstalk, 5-HT has been shown to modulate bacterial motility and induce the expression of virulence genes in bacteria via a quorum-sensing mechanism (Biaggini et al., 2015; Knecht et al., 2016). GF animals exhibit increased circulating tryptophan levels, which are corrected following colonization with a microbiota (Clarke et al., 2013). This was associated with elevated hippocampal 5-HT, which was not corrected by colonization. GF rats, on the other hand, have reduced circulating 5-HT levels (Wikoff et al., 2009), as well as reduced 5-HT in the hippocampus (Crumeyrolle-Arias et al., 2014). As the serotonergic system is involved in several human behavioral and physical maladies (see **Section VIII**), it has become ever more important to understand how the microbiota influence 5-HT along the microbiota-gut-brain axis.

Tryptophan can be diverted away from 5-HT production, into the kynurenine pathway. Indeed, it has been estimated that approximately 90% of available tryptophan is funneled towards the production of kynurenine (O'Mahony et al., 2015; Ruddick et al., 2006). This activity consists of several enzymatic steps that can differ depending on tissue type. For example, indoleamine-2,3-dioxygenase (IDO-1) is found in most tissues including the intestine, and tryptophan-2,3-dioxygenase (TDO) is found in the liver (Badawy, 2017). Kynurenine and its metabolites, including kynurenic acid and quinolinic acid, have been implicated in mental health (Cervenka et al., 2017; Schwarcz et al., 2012). In GF mice, there is reduced metabolism of tryptophan along the kynurenine pathway, which is likely partly responsible for the increased circulating availability of tryptophan (Clarke et al., 2013; Kennedy et al., 2017). Importantly, hepatic TDO is strongly regulated by glucocorticoids (Danesch et al., 1983; Ohta et al., 2017), while IDO is immune responsive. Since the microbiota modulates host circulating glucocorticoids and their production in response to stress (Sudo et al., 2004), as well as educating the immune system, the microbiota may indirectly affect host kynurenine production via glucocorticoid control of liver TDO (Badawy, 2017; O'Farrell and Harkin, 2017) or immune-based IDO activation (Strasser et al., 2017). Moreover, a correlation was seen between the reduction of *L. reuteri* in mice following chronic stress with an increase in serum kynurenine concentrations, mediated via a proposed mechanism based on bacterial-regulation of GI IDO via H_2O_2 production (Marin et al., 2017). This is consistent with the fact that kynurenine pathway enzymes such as IDO are sensitive to the redox environment (Gonzalez Esquivel et al., 2017).

In addition to the metabolic pathways leading to the production of 5-HT and kynurenine, microbial-derived indole derivatives of tryptophan are increasingly recognized as vital in the crosstalk between microbiota and host (Agus et al., 2018). For example, indole production from the bacterial metabolism of L-tryptophan can result in diverse changes in host physiology. It can be further metabolized by the host and/or microbial pathways into biologically active metabolites (Lee et al., 2015). Indeed, indole has been demonstrated to affect host intestinal epithelial barrier integrity (Bansal et al., 2010), modulate intestinal inflammation (Lamas et al., 2016) and protect against mortality following chemically-induced colitis (Shimada et al., 2013), as well as positively affect host longevity (Sonowal et al., 2017). In human feces, indole is detectable at micromolar concentrations (Darkoh et al., 2015), thereby warranting increased translational investigation of indole effects on host-microbe crosstalk in humans. Recently, microbial metabolites derived from tryptophan have been implicated in microglial control of astrocytes in the CNS (Dodd et al., 2017).

Indole-3-propionic acid and other biologically-active compounds are produced in the liver from microbiota-derived indole, supplied via hepatic portal circulation (Lee et al., 2015). Indole-3-propionic acid has also been reported to be produced by *C. sporogenes* (Dodd et al., 2017) and is usually undetectable in GF animals. GF mice were found to only have indole-3-propionic acid following colonization with *C. sporogenes* (Wikoff et al., 2009). Indole-3-propionate has been shown to affect host intestinal inflammation and to be reduced in patients with active colitis (Alexeev et al., 2018). Also, indole-3-propionic acid may affect other aspects of host physiology, including glucose metabolism (Abildgaard et al., 2018).

Isatin, another bacterial and host metabolite of indole (Gillam et al., 2000) has been demonstrated to affect anxiety-like behavior in rodents (Jaglin et al., 2018). Interestingly, isatin is detectable in a range of host tissues, including human cerebral spinal fluid and the hippocampus (Medvedev et al., 2007), and has been shown to be elevated in patients diagnosed with bulimia nervosa (Brewerton et al., 1995). Although isatin has been reported in micromolar concentrations in both blood and host tissues (Medvedev et al., 2007), the precise details of the pathway control points (be they microbial, host or at the host-microbe interface) leading from microbial-produced indole to the subsequent potential impact of isatin on host health, brain and behavior, such as anxiety, remain unclear. Indole metabolites have also been recognized to act on the aryl hydrocarbon receptor, a xenobiotic receptor distributed throughout the GI tract (Lee et al., 2015). Microbial-endocrinology-based media has recently been developed to study the production mechanisms of microbial neuroendocrine signals within different host-simulated environments (Villageliu et al., 2018) and may help shed some light on this important issue.

In addition to bacterial-derived indole and its byproducts, the gut microbiota is also associated with the production of tryptamine from tryptophan, a monoamine similar to 5-HT, and at least 10% of the human population have the necessary gut microbiota decarboxylases for this reaction (Williams, 2014). Although there are data from neuropharmacological and electrophysiological studies to suggest that it might activate postsynaptic receptors for tryptamine independent of those for 5-HT, its CNS function remains unclear (Jones, 1982). Much attention has been directed towards the GI tract, in which tryptamine activates the 5-HT_4 receptor expressed in the colonic epithelium to control colonic transit (Bhattarai et al., 2018; Cryan et al., 2018).

M. Branched Chain Amino Acids (BCAAs)

Branched-chain amino acids (BCAAs), such as valine, leucine, and isoleucine are considered essential amino acids because they cannot be synthesized *de novo* and must be obtained from the diet. They participate indirectly and directly in a variety of biochemical functions in the peripheral and central nervous systems (Brosnan and Brosnan, 2006; Fernstrom, 2005; Sperringer et al., 2017). These include protein synthesis, insulin secretion, energy production, brain amino acid uptake, and immunity in humans and animals. In addition, BCAAs are considered key nitrogen donors involved in inter-organ and intracellular nitrogen shuttling. The liver and skeletal muscle play a role in inter-organ shuttling of BCAA nitrogen, whereas in the brain intercellular shuttling is predominant (Sperringer et al., 2017). Although vital for normal physiological function, excessive amounts of BCAAs are considered toxic and can cause severe tissue damage, especially to the CNS, as evidenced from the neuropathology associated with maple syrup urine disease, an autosomal recessive metabolic disorder affecting BCAA levels (Menkes et al., 1954). Further, disruption of BCAA levels by branched chain ketoacid dehydrogenase kinase and SLC7A5 mutations has been shown to have extensive implications for survival and function of several neuronal circuits (Novarino et al., 2012).

BCAAs and other large neutral amino acids are transported quite readily across the BBB for transamination or delivery to neurons (Conway and Hutson, 2016; Oldendorf, 1971). However, the influx of leucine exceeds that of all others (Smith et al., 1987; Yudkoff, 1997). BCAAs also act as a regulator to promote intestinal development, nutrient transporters, and immune-related function.

Gut bacteria produce a higher proportion of BCAAs relative to the other amino acids but whether this influences host BCAAs availability remain to be determined (Dai et al., 2011; Neis et al., 2015), although a number of amino acids are altered in GF animals (Wikoff et al., 2009). Microbial-derived BCAAs include valerate, isobutyrate, and isovalerate. Notably, these bacterial metabolites have been shown to influence epithelial physiology and the mucosal immune system of the host (Blachier et al., 2007; Schaible and Kaufmann, 2005). It has been shown that the addition of BCAA's to trypticase yeast extract increases the yield of BCAA's in *Clostridia* (Elsden and Hilton, 1978) suggesting that amino acids can be used for SCFA and BCAA production by gut bacteria. Interestingly, supplementation with a BCAA cocktail has been shown to promote well-being and extend the lifespan of mice (D'Antona et al., 2010) similar to the benefits conferred by caloric restriction (Guarente, 2008; Valerio et al., 2011). A recent study showed that caloric restriction could establish a structurally balanced composition of the gut microbiota in mice indicating a potential association between caloric restriction, BCAA supplementation and the gut ecosystem (Zhang et al., 2013). Further, BCAA mixture supplementation has been shown to influence gut microbiota and metabolism (Yang et al., 2016). At 15 months of age, BCAA mixture -supplemented BALB/c mice compared with the control group was showed to display decreased *Bacteroidetes* and increased *Firmicutes* phyla (Yang et al., 2016). The decrease of Bacteroidetes phylum was related to reduced LPS-binding protein leading to reduced inflammation in BCAA mixture -supplemented mice (Raio and Phelps, 2015; Yang et al., 2016). Other findings have reported a strong relationship between changes in Firmicutes:Bacteroidetes ratio and obesity (Castaner et al., 2018). Interestingly, previous studies have found that BCAA supplementation modulates the expression of endogenous intestinal β-Defen-

sin, which can regulate porcine LPS (Ren et al., 2016). Consistent with the role BCAAs play in inflammatory disorders, acute amino acid starvation was reported to suppress intestinal inflammation via a mechanism dependent on the serine/threonine-protein kinase general-control-nonderepressible 2 (GCN2), an amino acid deficiency sensing enzyme (Ravindran et al., 2016). More recently, the role of amino acids was associated with assessing seizure susceptibility. Specifically, it was demonstrated that the restriction of peripheral ketogenic amino acids is necessary for mediating microbiota- and ketogenic diet-dependent increases in seizure resistance (Olson et al., 2018).

N. Bile Moieties

Bile acids are best known for facilitating the absorption of dietary lipids and lipid-soluble vitamins from the gut lumen. Primary bile acids are synthesized in the liver from cholesterol: cholic acid and chenodeoxycholic acid in humans, and cholic acid and α/β-muricholic acid in mice (Russell, 2003). After conjugation with either taurine or glycine, primary bile acids are released into the intestine to assist with lipid digestion and are recycled back into the liver (Thomas et al., 2008). Bile acids have been recognized as potent and versatile signaling molecules in and around the GI tract. By activating nuclear farnesoid X receptor (FXR) and plasma membrane TGR5 receptor, bile acids were shown to regulate systemic lipid, cholesterol, and glucose metabolism, as well as energy and immune homeostasis (Calmus and Poupon, 2014; de Aguiar Vallim et al., 2013; Thomas et al., 2008).

Recent advances in deciphering genome and metabolic capacities of the gut microbiota have shown bidirectional communication between the host bile system and gut bacteria, potentially leading to neural modulation. On the host side, bile acids help to limit the expansion of the bacterial population within the GI tract. Deficits in luminal bile acid levels have been associated with small intestine bacterial overgrowth, activation of inflammation, and subsequent damage to the epithelium (Inagaki et al., 2006; Lorenzo-Zuniga et al., 2003). Bile acids can exert antimicrobial effects directly, due to their membrane-solubilizing properties (Begley et al., 2005). Furthermore, by activating FXR signaling, bile acids can induce the expression of anti-microbial defense genes in the host (such as the inducible isoform of nitric oxide synthases - iNOS, and the antibacterial lectin - RegIIIγ) protecting the gut from epithelial deterioration and bacterial translocation (Inagaki et al., 2006; Joyce et al., 2014). These findings suggest that bile acids act as an important component of intestinal antimicrobial defense.

On the bacterial side, selective pressure of conjugated bile acids has favored the expansion of bile-metabolizing bacterial taxa in the human gut. Strikingly, all major gut-associated bacterial divisions, including *Lactobacillus*, *Bifidobacterium* and *Bacteroidetes* taxa, were shown to express bile salt hydrolase (BSH) enzymes which allow de-conjugation of bile acids from taurine and glycine (Begley et al., 2006; Jones et al., 2008). Bacteria with BSH activity have benefited from enhanced tolerance against bile and better survival in the gut environment (Begley et al., 2006; Devkota et al., 2012). The expansion of microbial BSH activity has increased the diversity of bile acids in the host (Joyce and Gahan, 2016). De-conjugated bile acids are less effectively re-absorbed from the small intestine and thus can leak into the large intestine, as recently reviewed (Hegyi et al., 2018). Numerous studies have explicitly demonstrated that bacteria-mediated transformation of host bile has a notable impact on host physiology, regulating bile acid and cholesterol metabolism, host energy

balance and weight gain (Hartmann et al., 2018; Pathak et al., 2018; Sayin et al., 2013; Wahlstrom et al., 2016).

From the perspective of microbiota-gut-brain signaling, the role of bile acids in the regulation of barrier function and immune status of the GI tract is of particular interest. Activation of TGR5 has generally been associated with anti-inflammatory effects and protective features towards the intestinal epithelium (Sarathy et al., 2017; Ward et al., 2017). The beneficial effects of TGR5 activation are at least in part mediated through direct action on the GI immune system (Biagioli et al., 2017; Cipriani et al., 2011; Haselow et al., 2013; Ichikawa et al., 2012). Multiple reports regarding TGR5 function (Gadaleta et al., 2011; Hartmann et al., 2018; Inagaki et al., 2006; Vavassori et al., 2009) have indicated that a very fine balance between host- and microbiota-produced bile acids is required to support epithelial barrier function and control the inflammatory response in the intestine. Maintenance of epithelial integrity is critically important not only for the gut but also for brain health (see **Section VIII**). To this end, alterations in gut microbiota composition which result in changes to the repertoire of bile acids present can have an impact on the gut-brain axis signaling via the inflammatory route of communication.

In support of this, it was recently shown that deficient bile acid de-conjugation was associated with impaired intestinal barrier function and behavior in a mouse model of ASD (the BTBR *T*$^{+}$ *Itpr3*^{tf}/J mouse) (Golubeva et al., 2017). Moreover, such changes were coincident with a substantial reduction in the relative abundance of bile-metabolizing bacterial taxa (*Bifidobacterium* and *Blautia*). An understanding of the bile-metabolizing capacities of specific probiotic strains would be important in parsing the relationships between bile and the brain. However, even though the two of the most widely used probiotic genera – *Bifidobacterium* and *Lactobacillus* species –demonstrate on average very high BSH activity, there are only scarce data available on their impact on host bile metabolism. For example, the multispecies VSL#3 probiotic (carrying *Lactobacillus* and *Bifidobacterium* strains) was shown to enhance bile acid de-conjugation and upregulate hepatic bile acid synthesis via the intestinal FXR/FGF15 signaling pathway (Degirolamo et al., 2014). BSH-active *L. reuteri* NCIMB 30242 reduced cholesterol levels and increased plasma bile acid levels in hypercholesterolemic subjects (Martoni et al., 2015).

Intriguingly, some recent evidence indicated that bile acids can affect the brain function directly. First, it has been shown that bile-induced activation of FXR/FGF signaling in the ileum can suppress hypothalamic AGRP/NPY (Agouti-related peptide/Neuropeptide Y) neurons in the brain through the centrally expressed FGF receptors, and markedly improve glucose tolerance in obese mice (Liu et al., 2018). It was further demonstrated that the murine olfactory system is capable of discriminating between male and female feces, based on sex-dependent differences in the fecal composition of bile acids (Doyle et al., 2016); some olfactory neurons were firing exclusively in response to either primary or secondary bile acid application. This suggests that bile acids can act as natural murine pheromones. Further studies are required to examine the possible link between gut microbiota, bile signaling and neural function, potentially implicating bile acids directly in gut-brain axis signaling.

O. Short-Chain Fatty Acids (SCFAs)

Perhaps the most examined gut microbial-derived metabolites are SCFAs, of which more than 95% consists of acetate, propionate and butyrate. SCFAs have been implicated in a variety of host processes including GI function (Gill et al., 2018), blood-pressure regulation (Pluznick, 2017), circadian rhythm (Tahara et al., 2018), and (neuro)immune function (Erny et al., 2017), even though their role in brain physiology and behavior has received less attention. Nonetheless, decreased fecal SCFA levels have been reported in various disorders where brain physiology and behavior are changed, including anorexia nervosa (Morita et al., 2015) and Parkinson's disease (Unger et al., 2016). In animal models, decreased gastrointestinal SCFA levels have been associated with Alzheimer's disease (Zhang et al., 2017a) (see **Section VIII**) and in some studies chronic stress, including (Maltz et al., 2018). Conversely, in humans, increased SCFA levels have been associated with obesity (Fernandes et al., 2014; Rahat-Rozenbloom et al., 2014; Schwiertz et al., 2010), chronic psychosocial stress in children (Michels et al., 2017) and ASD (Wang et al., 2012b). Although, a more recent report demonstrated decreased fecal acetate and butyrate levels in children with ASD (Liu et al., 2019). Such data implicates the potential of SCFAs to be a key player in microbiota-gut-brain axis communication, which we will explore in this section.

The primary source of SCFAs is the microbial fermentation of specific host-indigestible dietary fibers (Baxter et al., 2019; Macfarlane and Macfarlane, 2003), which is supported by the fact that GF animals and antibiotic treatment results in drastically lower SCFA levels (Backhed et al., 2007; Hoverstad and Midtvedt, 1986; Palleja et al., 2018; Zhao et al., 2016). Other sources of endogenous SCFAs include the breakdown of proteins by the microbiota (Yao et al., 2016), host metabolism of long-chain fatty acids and pyruvate into acetate (Knowles et al., 1974), as well as the consumption of alcohol (Sarkola et al., 2002). Finally, minor amounts of SCFAs can be attained by the consumption of fermented foods (Gill et al., 2018). Levels of SCFAs in human feces are approximately 60 g/kg for acetate, 10–20 g/kg for propionate and 3.5–32.6 g/kg for butyrate (Macfarlane and Macfarlane, 2003; McOrist et al., 2011), which is in line with the typically cited 60:20:20 ratio (den Besten et al., 2013). Gut-derived SCFAs are absorbed by the host epithelium, after which butyrate, in particular, is used as an energy source for colonocytes (Clausen and Mortensen, 1994; Hamer et al., 2008). The remainder of butyrate, as well as the majority of propionate, is subsequently metabolized by hepatocytes, resulting in 1- to 15- µmol/L concentrations of propionate and butyrate in circulation, whereas acetate is found within a range of 100–200 µmol/L (Bloemen et al., 2009; Cummings et al., 1987; Peters et al., 1992). This is supported by reports showing that exogenously administered SCFAs are metabolized in the same SCFA-specific preferential manner (i.e., butyrate > propionate > acetate) (Boets et al., 2017). As such, only acetate has been detected in cerebral spinal fluid (CSF) at approximate concentrations of 35 µmol/L (Nagashima et al., 2010), whereas no data on human physiological concentrations of propionate and butyrate in the brain or CSF has been published to our knowledge.

SCFA Uptake and Metabolism

SCFAs can diffuse through epithelia as non-ionized SCFA (Mascolo et al., 1991), or through transporters such as the pH-dependent hydrogen-coupled monocarboxylate transporter 1 and 4 (Kekuda et al., 2013; Tamai et al., 1995), the sodium-coupled monocarboxylate transporter 1 (Miyauchi et al., 2004), and, specifically for

butyrate, the liver organic anion transporter 7 (Shin et al., 2007). In the cell, SCFAs are mainly metabolized via the Krebs cycle as an energy source. This subsequently boosts mTOR (mammalian target of rapamycin), which is known to be an ATP and a homeostatic cellular energy sensor (Dennis et al., 2001) has been shown to be implicated in brain physiology (O'Riordan et al., 2014) and behavior (Xu et al., 2018).

Epigenetic Modulation of SCFAs

All SCFAs induce histone deacetylase (HDAC) inhibitory effects, with butyrate being the most potent inhibitor of class I and IIa HDACs (Cleophas et al., 2016; Davie, 2003). In addition, acetate can be converted to acetyl-CoA, which leads to increased histone acetylation (Soliman et al., 2012). Finally, SCFAs have recently been implicated in histone crotonylation, even though the relevance to brain physiology and behavior needs to be further investigated (Fellows et al., 2018).

Butyrate has been used as a tool for investigating the role of HDAC inhibition in brain physiology and behavior (for a comprehensive review covering this topic, see (Stilling et al., 2016)). This is usually achieved by acute intraperitoneal or subcutaneous administration of supraphysiological doses of butyrate, resulting in an immediate burst of increased histone acetylation. As such, studies using this methodology might not necessarily translate to gut microbiota-derived butyrate. These studies revealed that such an acute dose of butyrate enhances (re-)learning and memory, decreases depressive-like and perseverative behavior, and increases sociability in a mouse model of ASD (Bredy et al., 2007; Fischer et al., 2007; Kratsman et al., 2016; Levenson et al., 2004; Schroeder et al., 2007; Tsankova et al., 2006). It is also interesting to note that, using this method of administration results in a stress-like effect and increased anxiety-like behavior (Gagliano et al., 2014; Gundersen and Blendy, 2009). This might be explained by the fact that FFAR3 is expressed in the peripheral nervous system, activation of which results in increased sympathetic nervous system activity (Kimura et al., 2011).

SCFA Receptors

SCFAs can activate several G-protein coupled receptors (GPCR), of which free fatty acid receptor 2 (FFAR2, also referred to as GPR43) and 3 (FFAR3, also referred to as GPR41) are the most investigated (Brown et al., 2003; Le Poul et al., 2003; Nilsson et al., 2003). Expression of both receptors has been reported in the colon, various immune cells, and the heart. Only FFAR2 is expressed in adipocytes and skeletal muscle, whereas FFAR3 is expressed in the peripheral nervous system and the BBB (Hoyles et al., 2018; Koh et al., 2016). No expression of FFAR2 has been reported in the brain to our knowledge (Nohr et al., 2015).

A lesser-known colonic GPCR activated by butyrate is the receptor for niacin: hydroxycarboxylic acid receptor 2 (Thangaraju et al., 2009). Another receptor activated by butyrate is the olfactory receptor family 51 subfamily E member 1 (OR51E1 for humans, olfactory receptor 558 - Olfr558 for mice) (Priori et al., 2015). Importantly, since both receptors are activated by butyrate in higher micromolar to millimolar concentrations, it is unlikely that circulating butyrate could activate either of these receptors in non-gut or -liver tissue. The

only one activated by acetate and propionate is the GPCR olfactory receptor family 51 subfamily member 2 (OR51E2 for humans, olfactory receptor 78 – Olfr78 for mice) (Pluznick et al., 2013), which has been detected in the brain of rodents, but not humans (Yuan et al., 2001). It is clear that more work is needed to understand the relative contribution of these receptors especially at key time windows across the lifespan where their expression may vary, to microbiota-brain signaling.

SCFA-Induced Enteroendocrine Signaling

FFAR2, FFAR3, OR51E1, and Olfr78 are expressed by colonic enteroendocrine L cells (Fleischer et al., 2015; Karaki et al., 2006; Karaki et al., 2008; Priori et al., 2015; Tazoe et al., 2008), of which FFAR2 and FFAR3 activation results in the secretion of GLP-1 and peptide YY (PYY) into the peripheral circulation (Cherbut et al., 1998; Dumoulin et al., 1998; Psichas et al., 2015). Also, SCFA signaling stimulates the production of PYY in enteroendocrine cells, which is mostly mediated by HDAC inhibition (Larraufie et al., 2018). Importantly, acute delivery of propionate to the human colon using an inulin-propionate ester resulted in increased PYY and GLP-1 levels (Chambers et al., 2015), even though this was not replicated in a later study (Byrne et al., 2016). Interestingly, an infusion of acetate into the human distal, but not proximal colon, also results in increased circulating PYY, stressing the importance of spatial differences across the colon in regard to SCFA-induced enteroendocrine signaling (van der Beek et al., 2016).

Another well-studied hormone affected by SCFA-induced signaling is leptin, of which the secretion from adipocytes is enhanced following SCFA stimulation (Xiong et al., 2004; Zaibi et al., 2010). In addition, administration of butyrate to fasting mice results in elevated levels of GLP-1, GIP, PYY, insulin and amylin. The same was reported for propionate regarding GIP, insulin and amylin, whereas no effects were observed in acetate-treated mice (Lin et al., 2012). These data may implicate the diurnal variation of anorexigenic hormones (Fetissov, 2017), as SCFA levels also show a diurnal variation (Leone et al., 2015; Tahara et al., 2018), potentially involving SCFA-driven changes in anorexigenic hormones in daily host eating behavior. Interestingly, long-term supplementation of tributyrin, a butyrate prodrug, to high-fat diet (HFD) -induced obese mice, resulted in an amelioration of heightened leptin, resistin and insulin levels associated with obesity (Vinolo et al., 2012). In diet-induced obese, low-density-lipoprotein receptor transgenic mice, butyrate decreased insulin levels (Arnoldussen et al., 2017). As such, the acute administration of propionate and butyrate led to an increase in various anorexigenic hormones, while long-term supplementation decreased levels of such hormones in models of diet-induced obesity. Importantly, it has been reported that acetate promotes glucose-stimulated insulin and ghrelin secretion as well as obesity (Perry et al., 2016), which is in line with some reports indicating that obesity is associated with increased SCFA levels (Fernandes et al., 2014; Rahat-Rozenbloom et al., 2014; Schwiertz et al., 2010). As such, more research is needed regarding the mechanisms by which SCFAs affect host metabolism and endocrine systems, to achieve a better understanding of the exact role SCFAs play herein under conditions of increased endogenous SCFAs and SCFA supplementation.

Initial reports illustrated that SCFAs can stimulate the secretion of the neurotransmitter 5-HT into the lumen of the gut, as well as into the vasculature (Fukumoto et al., 2003). Later it was shown that the central, but not the orad or caudad compartment of the colon secreted 5-HT in response to SCFAs, highlighting once

again the importance of spatial differences across the colon (Grider and Piland, 2007)Nonesterified/*pharmacology</keyword><keyword>Intestinal Mucosa/drug effects/physiology</keyword><keyword>Kinetics</keyword><keyword>Muscle, Smooth/drug effects/physiology</keyword><keyword>Peristalsis/drug effects/*physiology</keyword><keyword>Physical Stimulation</keyword><keyword>Rats</keyword><keyword>Serotonin/*metabolism</keyword></keywords><dates><year>2007</year><pub-dates><date>Jan</date></pub-dates></dates><isbn>0193-1857 (Print. In addition, butyrate induces the secretion of 5-HT *in vitro*, which was not the case for acetate (Yano et al., 2015). Conversely, SCFAs failed to stimulate 5-HT secretion from primary mouse enterochromaffin cells (Martin et al., 2017). Further, SCFAs stimulate colonic TPH1 gene expression indicating increased 5-HT production (Reigstad et al., 2015; Yano et al., 2015). Overall, more research is needed to be performed on the mechanisms as to how SCFAs affect colonic, systemic and CNS serotonergic signaling, with an emphasis on spatial differences across the colon, including the 5-HT receptors, seeing that acetate has been shown to decrease 5-HT_{3B} expression (Bhattarai et al., 2017).

SCFA-induced Vagus Nerve Activation

It is well established that SCFAs can activate the PNS, where FFAR3 receptor has been detected in the enteric neural plexus, the portal nerve and autonomic and sensory ganglia (De Vadder et al., 2014; Kaji et al., 2016; Nohr et al., 2015; Won et al., 2013). Also, Olfr78 has also been detected in the PNS (Pluznick et al., 2013). Locally, in the gut, FFAR3 is expressed on nitrergic and cholinergic enteric neural plexuses (Kaji et al., 2018; Kaji et al., 2016). Interestingly, butyrate can increase the proportion of myenteric cholinergic neurons through HDAC inhibition (Soret et al., 2010), indicating that SCFAs might play a role in the homeostasis of ENS physiology. Particularly important for gut-brain axis signaling, activation of FFAR3 on the vagus nerve innervating the portal vein results in increased neuronal activity in the dorsal vagal complex, parabrachial nuclei and hypothalamus (De Vadder et al., 2014). Even though oral administration of butyrate to fasting mice results in decreased neuronal activity in the NTS and dorsal vagal complex, as well as decreased activity of orexigenic NPY-positive neurons in the hypothalamus, indicating a dynamic regulation of SCFAs on hypothalamic neuronal circuitry (Li et al., 2018c). Overall, it is clear that SCFA-induced vagus nerve signaling results in the activation of various neurons in the central nervous system. However, more research needs to be performed investigating which specific neuronal populations are activated by SCFAs-induced vagus nerve signaling throughout the brain and how this relates to behavior.

SCFAs and Host Systemic Immunity

SCFAs have been implicated in the first line of defense between the microbiota and host intestinal barrier permeability. First of all, SCFAs can enhance the mucosal barrier through the stimulation of mucus production (Barcelo et al., 2000; Finnie et al., 1995; Jung et al., 2015; Willemsen et al., 2003), which is likely mediated through FFAR3 (Said et al., 2017). In addition, SCFAs have been demonstrated to alleviate impairments in epithelial barrier integrity by stimulating tight junction assembly (Peng et al., 2009; Tong et al., 2016; Wang et al., 2012a). Further, SCFAs have been shown to modulate immune cells themselves (Correa-Oliveira et al., 2016; Kim et al., 2014). These include the regulation of neutrophils chemotaxis and inflammation (Le Poul et al., 2003; Vieira et al., 2017; Vinolo et al., 2011), the suppression of cytokine production from myeloid cells (Nastasi et al., 2015; Park et al., 2007) and by regulating T regulatory, T helper 1, and T helper 17 cell differ-

entiation (Al Nabhani et al., 2019; Asarat et al., 2016; Park et al., 2015; Smith et al., 2013; Tan et al., 2016). Overall, SCFAs influence the immune system in an anti-inflammatory manner.

SCFAs: Direct Effects on the Brain?

Current research indicates that gut microbial-derived SCFAs might be able to affect brain physiology through direct interactions. Specifically, acetate has been reported to be present in the cerebrospinal fluid, and gut microbial-derived acetate has been shown to reach the brain and trigger PNS signaling (Nagashima et al., 2010; Perry et al., 2016). It is therefore interesting to note that acetate signaling in the hypothalamus promotes an expression profile of regulatory neuropeptides that favor appetite suppression (Frost et al., 2014).

Considering the relatively low levels of propionate and butyrate in the circulation, whether these SCFAs can directly impact the brain is still very much uncertain. However, it is important to note that a propionate concentration as low as 1 μM can affect the BBB, indicating that physiologically relevant SCFAs could potentially impact the brain (Hoyles et al., 2018). Notably, a study tracing radio-labeled butyrate in primates found that only 20% remained after 5 minutes post-administration, with the brain only taking up less than 0.006% (Kim et al., 2013). As such, more research needs to be performed to validate whether gut microbial-derived propionate and butyrate can directly affect brain physiology.

Gut-Derived SCFAs, Brain Physiology, and Behavior

As stated earlier, SCFAs have been shown to ameliorate deficits in microglia morphology and immaturity as seen in GF mice (Erny et al., 2015). In addition, FFAR2 transgenic mice have severely malformed microglia even though microglia do not express FFAR2, indicating that FFAR2 plays an indirect role in microglia function and homeostasis (Erny et al., 2015). GF mice also have increased BBB permeability, which can be rescued by SCFAs (Braniste et al., 2014). Interestingly, the latter study also reported that butyrate rescued deficits in histone acetylation in the frontal cortex of GF mice (Braniste et al., 2014). This is in line with previous reports showing that butyrate supplementation in drinking water increased brain histone acetylation (Bonthuis et al., 2011; Minamiyama et al., 2004)

Pigs supplemented with butyrate have increased hippocampal granular cell layer volume, hippocampal neurogenesis and altered hippocampal glucose metabolism (Val-Laillet et al., 2018). In addition, 9-month old, but not 12-month old diet-induced obese, low-density-lipoprotein receptor transgenic mice have decreased hippocampal cerebral blood flow and functional connectivity, spatial memory, and increased hippocampal microglia activation, all of which were rescued by butyrate supplementation (Arnoldussen et al., 2017). Acute and targeted administration of propionate to the human colon using an inulin-propionate ester results in a reduced anticipatory reward response to high-energy foods in the striatum (Byrne et al., 2016). Furthermore, intrarectal administration of propionate in rats undergoing chronic unpredictable mild stress ameliorates deficits in reward-seeking and anxiety-like behaviors (Li et al., 2018b). Also, pigs supplemented with butyrate have increased glucose metabolism in the nucleus accumbens (Val-Laillet et al., 2018).

Overall, data from GF mice indicates that SCFAs play a role in the maintenance of homeostasis within the CNS. In addition, particularly the hippocampus and striatum seem to be affected by gut-derived SCFAs, indicating that SCFAs may play a modulatory role in learning and cognition (Arnoldussen et al., 2017; Val-Laillet et al., 2018), as well as reward-associated behaviors (Byrne et al., 2016; van de Wouw et al., 2018). A recent study has shown that supplementation of a mix of the principle SCFAs (i.e., acetate, propionate, and butyrate) in drinking water ameliorated long-lasting psychosocial stress-induced HPA axis hyperactivity, intestinal permeability and alterations in anhedonia in mice (van de Wouw et al., 2018). Also, SCFAs decreased anxiety- and depressive-like behavior in selective behavioral tests, which was not present when mice had previously undergone psychosocial stress. This was accompanied by decreased gene expression of the mineralocorticoid receptor in the hypothalamus, hippocampus, and the colon, as well as decreased CRF receptor 1 and 2 in the colon. Such data further implicate SCFAs in stress-related disorders and reinforce the role SCFAs play in microbiota-gut-brain axis communication (van de Wouw et al., 2018).

It is worth noting that not all of the effects of SCFAs on behavior have been positive. For instance, increased SCFA levels have been implicated in the pathophysiology of Parkinson's disease in mice (Sampson et al., 2016). In addition, intraventricular infusions of propionate result in increased repetitive behaviors, impaired sociability, epileptic and convulsive responses and is therefore used a reliable model of autism spectrum disorder (MacFabe et al., 2007; MacFabe et al., 2011). As such, the authors of these latter studies hypothesized that one of the underlying mechanisms in ASD pathophysiology is an overproduction of propionate by the gut microbiota, resulting in elevated propionate levels in the brain and contributing to the ASD phenotype (MacFabe et al., 2007). However, more research is needed to understand whether propionate can influence the brain directly and whether this results in the same phenotype as that found in intraventricular propionate infusion-induced ASD.

P. Spinal Mechanisms

From an anatomical perspective, it is usually described that there are two distinct neuroanatomical routes for neural signaling from the intestine to the brain with the non-painful (satiety, distension, motility and other homeostatic functions) mediated predominantly by vagal/ pelvic innervation as described previously, and the painful sensory stimuli conveyed by splanchnic innervation (Vermeulen et al., 2014). However, it must be stated that the sensory tone of these signaling pathways is not mutually exclusive, and that physiological events relating to the status of the gut including distension, motility, inflammation, pain, pH change, cellular damage or temperature (Brookes et al., 2016) can also be transmitted through spinal splanchnic innervation via NTS of the brainstem (Christianson et al., 2009; Ren et al., 1989) to higher centers in the brain.

Stimuli associated with pain, inflammation, discomfort, and injury are carried through spinoreticular, spinomesencephalic, spinohypothalamic and spinothalamic tracts to the brain (Millan, 2002), and the specific role of the GI microbiota in visceral pain response will be discussed further later (**Section VIII.L.)** The spinoreticular tract projects to the dorsal reticular nucleus in the brainstem to regulate the affective-motivational component of pain. The spinomesencephalic tract relays information about the intensity and location of

the painful stimulus to the periaqueductal gray and other brain regions. In contrast, the spinohypothalamic tract communicates with the hypothalamus, which together with other neuroanatomical loci co-ordinates emotional, autonomic and behavioral responses to the nociceptive information, mediating the sensation of pain, heat, cold and touch (Millan, 2002). The thalamus functions as a relay station where multiple somatic and visceral information converge. Once the information has been processed, further inputs are conveyed to cortical regions including the anterior cingulate cortex, the insula and somatosensory cortex to be interpreted as a painful stimulus. Once the nociceptive information has been processed, the descending pathways (from brain to spinal cord) can exert an inhibitory or facilitatory effect on the sensation of pain. However, under normal physiological conditions, at the level of the spinal cord, the neurons involved in nociception are under 'gated' control. Until a certain threshold of stimulation is surpassed, these neurons are quiescent, and no nociceptive information is propagated to supraspinal sites.

Q. Hypothalamic-Pituitary-Adrenal (HPA) Axis

The HPA axis is one of the main neuroendocrine systems in the human body and one of the key non-neuronal routes of communication within the microbiota-gut-brain axis. It is best known as the principal neuroendocrine coordinator of the response to stress (Mayer, 2000). Upon disturbance of homeostasis, corticotrophin releasing factor (CRF) is released from paraventricular nucleus (PVN) of the hypothalamus, stimulating the release of adrenocorticotrophic hormone (ACTH) from the anterior pituitary (**Fig. 4**). This hormone is secreted into systemic circulation and targets the adrenal cortex, ultimately resulting in a release of glucocorticoids (de Wied et al., 1993). Once in systemic circulation, they are distributed throughout the body. In the brain, glucocorticoids interact with high-affinity mineralocorticoid receptors and lower affinity glucocorticoid receptors (Herman et al., 2016; Smith and Vale, 2006; Tsigos and Chrousos, 2002). The primary function of the HPA axis activation is to prime the body for the 'fight or flight' response (Mayer, 2000). One of the main outputs is negative feedback in which glucocorticoids act back on the hypothalamus and pituitary gland inhibiting adrenal secretion. At the same time, the activity of the (PVN is regulated by multiple afferent sympathetic, parasympathetic and limbic circuits (Smith and Vale, 2006).

Connecting the Microbiota to the HPA Axis

The seminal research linking the gut microbiota to the HPA axis has come from work with GF mice (see **Table 2**). In response to restraint stress, male GF mice exhibited a hyper-responsive HPA axis, characterized by elevated levels of plasma corticosterone (Clarke et al., 2013; Sudo et al., 2004) suggesting that the exposure to microbiota has a specific timeframe of functionality (Sudo et al., 2004). Alterations in hippocampal NMDA and 5-HT_{1A} receptor mRNA expression have also been recorded in GF mice (Neufeld et al., 2011). Both of these receptors are known to influence CRF release from the hypothalamus and changes in their expression may contribute to altered HPA function in GF animals. In humans, patients with irritable bowel syndrome had exaggerated ACTH and cortisol responses to CRF infusion (Dinan et al., 2006) together with an altered microbiota (Eisenstein, 2016; Grenham et al., 2011). It is clear that although the microbiome regulates the HPA axis, the opposite is also true. In animal models of stress with HPA axis alterations, there are marked changes in microbiota composition (see **Section VII. H.** and **Table 2**).

Dialogue between the HPA Axis and Other Pathways of Microbe to Brain Communication

The HPA axis interacts with other non-neuronal as well as neuronal pathways of communication between the gut and the brain. Interestingly, there is an interplay between the vagus nerve and the HPA axis. In rodents, vagal stimulation increased the expression of CRF mRNA in the hypothalamus (Hosoi et al., 2000). Furthermore, plasma levels of ACTH and corticosterone were strikingly elevated after vagal stimulation.

Immunity-HPA axis interactions are implicated in a variety of stress and inflammatory disorders; thus it is not surprising that such cross-talk may also affect microbiota-gut-brain signaling. In animal models of psychological stress, gut permeability is increased, and translocation of native bacteria into the host occurs (Demaude et al., 2006). Activation of the mucosal immune response via exposure to bacteria and bacterial antigens beyond the epithelial barrier induces pro-inflammatory cytokine secretion and ultimately activates the HPA axis. In the absence of the resident microbiota, members of the TLR family have low or absent expression profiles in the gut, thus compromising appropriate neuroendocrine responses to pathogenic threats (O'Hara and Shanahan, 2006). In TLR4 transgenic mice, activation of the HPA axis in response to Gram-negative bacteria is absent (Gosselin and Rivest, 2008). Although much has been learned from these and other important studies linking the microbiota to HPA activity, it is evident that more scrutiny needs to be placed on this influential relationship.

R. Peptidoglycans

Pattern recognition receptors (PRRs), as their name suggests, detect distinct microbial patterns or structures of microorganisms such as proteins, lipids, glycans and nucleic acids (amongst others) known as pathogen-associated molecular patterns (Qureshi et al., 1999), for example, LPS (Raio and Phelps) on the surface of gram-negative bacteria and peptidoglycan (PGLN) on the surface of gram-positive bacteria (Medzhitov, 2007). Consisting of sugars and amino acids, PGLN are a critical part of most bacterial cell walls**.** The thickness of the bacterial cell wall is governed by the thickness of the peptidoglycan. In Gram-positive bacteria the cell wall can be between 20 and 80 nm thick whereas in Gram-negative bacteria it is much thinner, measuring 7 to 8 nm (Costerton et al., 1974). Throughout evolution, multicellular organisms were required to develop the capacity to differentiate self from non-self, given the large number of microorganisms in the environment, the host had to evolve a controlled and specific structural recognition of these bacterial cell wall components (Rogers and Perkins, 1980; Vollmer et al., 2008). Similarly, PGLN is a large polymeric molecule which structurally is similar between organisms, but critically the core sugar backbone is made of repeating disaccharides, which vary significantly between bacterial species (Schleifer and Kandler, 1972; Vollmer et al., 2008). This sugar backbone is also cross-linked with amino-acid side chains, which can be cross-linked in different confirmations, adding an additional layer of complexity (Vollmer et al., 2008).

The innate immune system has evolved to detect both complete and fragmented peptidoglycan using numerous PRRs both intracellularly and at the cell surface (Medzhitov, 2007), (Kawai and Akira, 2009). There are four peptidoglycan recognition proteins (PGLYRP 1-4) which bind to peptidoglycan in bacterial cell walls

via recognition of the muramyl pentapeptide (or tetrapeptide) structures (Royet et al., 2011). Interestingly, PGLYRPs are also capable of binding LPS using different binding sites to those used for binding PGLN, meaning they can bind to both Gram-positive and Gram-negative bacterial cell walls (Royet et al., 2011). The exact method by which PGLYRPs induce cell death through binding to PGLN are unclear, but it is thought to be facilitated by the activation of enzymes that induce oxidative and stress response cell suicide (Kashyap et al., 2017; Kashyap et al., 2014). Interestingly, a recently discovered anti-inflammatory protein, Micro Integral Membrane Protein, found on the surface of *L. Plantarum*, has been shown to enhance gut barrier function and can modulate microbiota and inflammatory cytokines (Yin et al., 2018).

The gut microbiota is an important source of PGLN where it translocates from the mucosa to the systemic circulation under physiological conditions (Clarke et al., 2010). In the circulation it has been found to interact with bone-marrow-derived neutrophils, a cell not normally observed in the gut, indicating that PGLN may be present also at body sites far removed from the gut (Arentsen et al., 2017). Interestingly, these studies revealed that PGLNs and their receptors from commensal microbes resident in the gut were present in the brain of normal developing mice. The PRR nucleotide-binding oligomerization domain-containing protein-1 (Nod1) which identifies meso-2,6-Diaminopimelic acid -containing PGLN was recognized as the key regulator of the systemic effects of PGN. Moreover, these results suggest that PGLN can cross the BBB under normal conditions and that viral or bacterial infection is not required for this breach. PGLYRP-2 was highly expressed (along with Nod1) in neurons implying that PGLN may influence neurons directly (Arentsen et al., 2017). While PGLYRPs have predominately been implicated in innate immunity, their role in behavior has also recently been explored. In the bacterial peptidoglycan sensing molecule Pglyrp2-transgenic mouse, major sex-dependent alterations of motor and anxiety-like behaviors in aged mice were observed. Furthermore, there were subtle alterations of synaptic-related gene expression in brain regions associated with the processing of emotional stimuli (Arentsen et al., 2018). This data suggests that bacteria are sensed by the innate immune system and may affect brain function and development.

VIII. Microbiota and Synaptic Plasticity

Neuroplasticity is an important aspect of neural function in both the GI tract and the brain, and as a result, should be a crucial consideration when examining microbiota-gut to brain communication processes. However, the extent that the microbiota can exact long-lasting neuroplastic changes in the host's gut or brain is understudied, and currently unresolved. In the following section, we examine what the current state of the field is and identify important future potential avenues of study.

One important and well-characterized method of measuring any potential long-term effects of microbial influence on the innervation of the gut, and neural network of the brain, is through the measurement of synaptic plasticity. Plasticity specifically refers to a long-lasting change to a system, with a specific functional purpose. Plasticity of the synapse involves alteration of the synaptic strength, where increased or decreased neuronal activity results in long-lasting changes in synaptic weights distributed throughout a network (Bliss and Lomo, 1973). Much work has been performed studying synaptic plasticity of the CNS, but recently it has become ever more apparent that neuronal plastic changes also occur in the ENS (Demir et al., 2013; Lomax et al., 2005). In the following section, we will examine what is known and what future directions are most

compelling.

A. Synaptic Plasticity in the CNS

From initial observations by Ramón y Cajal over a century ago (Jones, 1994), to the development of Hebb's rule in 1949 (Hebb et al., 1994), with first experimental evidence emerging from seminal work by Eric Kandel and colleagues soon after (Byrne et al., 1978; Castellucci et al., 1978), investigating synaptic plasticity has long been at the forefront of our quest to understand the mechanisms of the working brain. CNS synaptic plasticity specifically refers to the cellular molecular and physiological processes underlying cognitive and emotional behavioral phenotypes such as learning and memory (Bailey et al., 2015). In the brain, activity-dependent modification of the synapse is believed to be pivotally involved in the brains capacity to assimilate transient experiences to form perseverant memory engrams (Citri and Malenka, 2008). Here, an activity-dependent persistent strengthening of synaptic efficacy is described as long-term potentiation (LTP) (Madison et al., 1991). In the widely studied unidirectional tri-synaptic excitatory pathway of the rodent hippocampus (Knierim, 2015), any significant enhancement in synaptic efficacy lasting at least an hour after a conditioning stimulus is believed to be LTP (Nicoll, 2017). LTP is used as an indicator of healthy brain function and is impaired in many rodent models of neurodegenerative disease (Nicoll, 2017). Further, deficits in LTP usually accompany cognitive dysfunction (Li et al., 2015; Lin et al., 2014; Wiescholleck and Manahan-Vaughan, 2013), and it is regarded as a reliable, functional readout for neurophysiological processes.

A change in the state of plasticity can involve presynaptic, postsynaptic or extrinsic factors modifying the synapse. These changes can be short-lived, resulting in a more dynamic synaptic state, or long-term, resulting in a change in synaptic efficacy that can last for several months if not longer (Kandel et al., 2014). Synaptic plasticity in the brain is particularly vulnerable to disruption by factors that alter cognition in neurological and psychiatric disease. Examples of processes that involve alteration of synaptic plasticity include synaptic remodeling (Ziv and Brenner, 2018), synaptogenesis (Bednarek and Caroni, 2011), axonal sprouting/ pruning and dendritic remodeling (Selemon, 2013), as well as (neurogenesis) and recruitment (Ganguly and Poo, 2013) many of which have been shown to be influenced by gut microbes (984). Most importantly, any sensory, motor, inter or CNS neuron-neuron connection is a synaptic connection. Therefore, any mechanism that can alter the plasticity of the synapse can be considered as having a potential impact on the phenotype associated with the synapses involved; in the CNS neuronal synapse, this includes cognitive and emotional phenotypes. For example, the hippocampus is highly responsive to glucocorticoids (Lupien et al., 2005), which can be metabolized by the microbiota (Ridlon et al., 2013) into the steroid and pro-hormone 11β-hydroxy-androstenedione (11β-OHAD) (Bokkenheuser et al., 1984; Ridlon et al., 2013). Hormone binding to receptors in the CA1 region of the hippocampus leads to multiple cellular responses, including changes in synaptic function and, in excess, neuronal injury (Chen et al., 2006). Many models of microbiota perturbation have been used in the study of synaptic plasticity and cognitive function. However, in totality, this area has lagged behind other physiological or behavioral readouts in parsing the role of the microbiome in brain function.

Germ-free animal studies of CNS and the implications for synaptic plasticity and behavior

GF animals have been utilized in examining the involvement of the microbiota in CNS synaptic plasticity (see **Table 2**). However, for perhaps logistical reasons for setting an electrophysiological rig within a germ-free setting there has been limited direct plasticity measures published. Nonetheless, GF animals have altered expression of genes implicated in neurophysiology in the amygdala (Stilling et al., 2015) and hippocampus (Chen et al., 2017a) (see **Table 2**). This ultimately leads to an altered transcriptional profile, combined with a marked increase in immediate-early gene (Fos, Egr2, Fosb, Arc) expression in the amygdala (Hoban et al., 2018), as well as enhanced expression of gene splicing factors and alternative exon usage (Stilling et al., 2018). A recent study, utilizing the GF mouse model, linked maternal diet, gut microbiota imbalance, and ventral tegmental area plasticity with behavior modifications (Buffington et al., 2016).

BDNF is an important plasticity-related protein. It has been shown to be involved in synaptogenesis (Cunha et al., 2010) and neurogenesis (Taliaz et al., 2010), as well as restoring LTP in aged rats when overexpressed (Rex et al., 2006), but see (Edelmann et al., 2014). Moreover, BDNF is believed to play an important role in anxiety and depression in humans and has been reported to be expressed in lower than normal levels in the GF mouse cortex and hippocampus (Clarke et al., 2013; Diaz Heijtz et al., 2011). The gut microbiota have been shown to directly moderate brainstem and hypothalamic expression of BDNF, where conventionally raised mice differed significantly from GF mice (Schele et al., 2013). Moreover, studies from Gareau and colleagues showed BDNF expression as measured by immunohistochemistry was decreased in the CA1 hippocampal brain area in GF stressed mice compared to stressed controls (Gareau et al., 2011). GF studies also show that microbes can also regulate NMDA receptors (NMDAR) (Neufeld et al., 2011), and these proteins have an important role in brain development and neural plasticity (Bercik et al., 2010; O'Sullivan et al., 2011; Sudo et al., 2004). Further studies into microbiota driven modulation of neuronal NMDAR and BNDF expression are warranted.

Antibiotics in animal studies of the CNS and implications for synaptic plasticity and behavior

As previously stated, antibiotic-induced ablation of the gut microbiota in rodents results in long-term effects on neurochemistry and behavior (Champagne-Jorgensen et al., 2019; Desbonnet et al., 2015; Guida et al., 2018; Neufeld et al., 2011) (see **Table 3**). In a recent long-term treatment regime, application of a broad-spectrum antibiotic for seven weeks (Mohle et al., 2016) resulted in behavioral deficits in the hippocampus-reliant novel object recognition (NOR) task as well as decreased neurogenesis. These deficits were corrected with adoptive transfer of Ly-6chi monocytes into antibiotic-treated animals, coupled with access to a running wheel (voluntary exercise), or probiotic treatment. In another study, two weeks of antibiotic cocktail administration resulted in marked changes in hippocampal BDNF tropomyosin receptor kinase B (TrkB) signaling, transient receptor potential vanilloid 1 (TRPV1) phosphorylation and overall heavily reduced hippocampal CA3-CA1 synaptic activity. This was somewhat ameliorated by treatment with the probiotic *L. casei* DG probably via a gut anti-inflammatory mechanism (Guida et al., 2018). Results such as these demonstrate that neurogenesis (Ogbonnaya et al., 2015; Sawada et al., 2018), apoptosis, and synaptic pruning, and hence synaptic plasticity, can be regulated by microbiota signaling.

Prebiotics, probiotics and CNS implications for synaptic plasticity and behavior

A number of studies have shown that administration of pre- or probiotics can alter components of neuroplasticity (see **Section II** and **Tables 4, 5**). Indeed, the prebiotic B-GOS® elevated rat brain NMDAR levels (Savignac et al., 2013) and enhanced cortical responses to PFC-NMDAR activation. The electrophysiological phenotype induced by the prebiotic was consistent with improved behavioral attentional set-shifting and increased cortical glutamate [NMDA] receptor subunit epsilon-2(GRIN2) A/B-containing populations of NMDAR's (Gronier et al., 2018), rather than increased cortical glutamate levels per se (Savignac et al., 2013). Further, prebiotics and probiotics were recently shown to act therapeutically in middle-aged rats, improving spatial memory (Romo-Araiza et al., 2018).

The potential for coordinated hypothalamic synaptic plasticity modulation by a probiotic combination has also recently been shown. The combination treatment of *B. longum* (R0175) and *L. helveticus* (R0052) on neural plasticity genes, hypothalamic BDNF was increased whereas Growth Associated Protein 43 (GAP43), GFAP (glial fibrillary acid protein), Vim (vimentine), Syt4 (synaptotagmin), Snap25 (synaptic-associated protein 25 kDa) and cell adhesion markers (Reln, Sema [semaphorine]) were all decreased relative to a stressed control cohort (Ait-Belgnaoui et al., 2014). Hippocampal NMDAR expression was also increased in the DG and CA1 following daily consumption of the probiotic *L. fermentum* strain NS9, which also enhanced radial maze memory compared to antibiotic-treated rat (Wang et al., 2015). In a seminal *in vivo,* hippocampal electrophysiology experiment neurophysiological and behavioral impairments in a diabetic rat model of diabetes mellitus were rescued with the probiotic treatment of *L. acidophilus*, *B. lactis* and *L. fermentum* (Davari et al., 2013).

A novel probiotic formulation of *bifidobacteria* (SLAB51) partially restores deficits in autophagy and the ubiquitin-proteasome system, two neuronal proteolytic pathways that influence neuroplasticity in a mouse model of AD (3xTg-AD) (Bonfili et al., 2017). Moreover, chronic administration of *L. rhamnosus* (JB-1) induced region-specific alterations in $GABA_{B1b}$ and $GABA_{A\alpha2}$ mRNA (Bravo et al., 2011). Further, *L. rhamnosus* and *B. longum* reversed antibiotic-induced reductions in $GABA_A$ receptor α5 and δ subunits in the juvenile rat hippocampus (Liang et al., 2017). One further study found that *L. reuteri*, could reverse observed social behavior deficits and restore hypothalamus oxytocin immunoreactive neurons to control levels as well as correct deficits in synaptic plasticity (Zhu et al., 2017).

Interestingly, memory dysfunction observed following short-term colitis, induced via infection with *Citrobacter (C.) rodentium,* was prevented following daily probiotic (mixture composed of an *L. rhamnosus* and *L. helveticus*) administration (Gareau et al., 2011). These changes were coincident with changes in BDNF and c-Fos modulation in the hippocampus. Synbiotic approaches (combining specific potential probiotics with prebiotics) have also been utilized to investigate the effect of microbiota on synaptic plasticity. In a combined pre/pro-biotic study, *L. casei* and inulin fed rats enhanced 5-HT_{1A} mRNA levels in the DG and CA1 areas of the hippocampus in healthy juvenile rats, indicating an early behavioral change as a direct result of synbiotic

administration (Barrera-Bugueno et al., 2017).

Multispecies approaches have also been used to examine brain plasticity modulation via microbiota**.** A recent study utilized a probiotic mixture comprising eight different gram-positive bacterial strains, VSL#3, which is believed to have an anti-inflammatory effect (Mimura et al., 2004)-(Kim et al., 2003; Reiff et al., 2009) and reduce pain in an animal model of visceral hypersensitivity (Distrutti et al., 2013)Wistar</keyword><keyword>-Real-Time Polymerase Chain Reaction</keyword><keyword>Visceral Pain/etiology/*prevention & control</keyword></keywords><dates><year>2013</year></dates><isbn>1932-6203 (Electronic. VSL#3, which contains *Streptococcus (S.) thermophilus* DSM24731, *B. breve* DSM24732, *B. longum* DSM24736, *B. infantis* DSM24737, *L. acidophilus* DSM24735, *L. plantarum* DSM24730, *L. paracasei* DSM24733, *L. delbrueckii* subspecies *Bulgaricus* DSM24734, was shown to rescue age-related deficits in LTP (Distrutti et al., 2014). VSL#3 was also able to modulate the expression of a cohort of genes in the cortex associated with age-related decline. Here, they witnessed an increase in hippocampal BDNF and synapsin expression, suggesting that VSL#3 exerted a neuro-synaptotrophic effect. This is consistent with the fact that VSL#3 acted as an anti-inflammatory in the mouse gut, which was mirrored in the brain, as noted by a reduction in CD11b and CD68 mRNA expression (two markers of microglial activation) in the hippocampus in VSL#3-treated aged rats (Distrutti et al., 2014). While it is obvious that gut microbiota can influence central neuroplasticity, much has yet to be discovered, especially in terms of mechanistic insight and whether microbiota interventions have a clinically relevant therapeutic option for modulating neuroplasticity in humans

S. Synaptic Plasticity in the ENS

As previously mentioned (**Section IV**.), the ENS encompasses a large part of the ANS. Due to the organization and structure of the number, morphology, and neurochemical nature of the ENS networks within the ANS, it is believed to be more analogous to the CNS than other networks within the peripheral nervous system (Gershon, 2018; Timmermans et al., 1997; Wood, 2008, 2016)**.** Much like the CNS, the ENS maintains its capacity to adapt and reorganize its synapses throughout the host's lifetime, similar to synaptic plasticity in the CNS (Demir et al., 2013; Lomax et al., 2005)**.** It has been shown that enteric ganglia share some morphological similarities to CNS astrocytes (Jessen and Mirsky, 1983), which lie adjacent to enteric neuronal cell bodies, which are very much like glia in the CNS (Yoo and Mazmanian, 2017).

One specific example of ENS plasticity includes increased sensitivity at sensory nerve terminals in the gut, either directly or indirectly, by both chemical and mechanical stimuli (Grundy et al., 2006). It is possible that bacterial infections can enhance pain signaling and induce a plastic state in the gut by directly activating sensory neuron afferents and modulating inflammation (Chiu et al., 2013). It is believed that plasticity of a heightened pain response, known as central sensitization, contributes to chronic pain. The processes are remarkably similar to LTP in the hippocampus where increased synaptic transmission, and hence sensory neuronal plasticity, can be promoted via the application of glutamate (Larsson and Broman, 2011), substance P (Yu et al., 2016) or calcitonin gene-related peptide (CGRP), (Iyengar et al., 2017), onto ascending excitatory pathways, leading to CNS sensitization on second-order spinal neurons. However, an unintended consequence of enhanced signaling and sensitization promotes abnormal processing of pain (see **Section**

VIII. L.). Interestingly, *L. reuteri* (DSM 17938) has been shown to attenuate jejunal spinal nerve firing evoked by distension or capsaicin via TRPV1 channel recruitment (Perez-Burgos et al., 2015).

It is worth contextualizing some of the commonalities between plasticity in CNS and ENS. An important neurodevelopment and plasticity-related protein growth-associated protein-43 (GAP-43) is expressed in both the CNS and the ENS; it is found in high levels throughout the lifespan in the hippocampus (Simmons et al., 2008), as well as in the myenteric and submucous ganglia (Giaroni et al., 1999; Stewart et al., 1992). Further, the neurotransmitter vasoactive intestinal peptide (VIP), which is involved in pre- and postsynaptic GABAergic enhancement to hippocampal interneurons, resulting in an increase of excitatory synaptic transmission in hippocampal pyramidal cells (Cunha-Reis et al., 2004; Yang et al., 2009), a process involved in the expression of LTP, is also present in inhibitory muscle motoneurons (Benarroch, 2007). Another CNS active neurotransmitter, acetylcholine, is active at excitatory enteric motoneuron synapses (Zhu et al., 2011). Further, the neurotransmitter dopamine is also found in both the central and enteric nervous systems (Gershon, 2018; Li et al., 2006). It has been suggested that enteric crest-derived stem cells, believed to be largely responsible for synaptic plasticity in the ENS, could one day be used to seed the CNS in order to mitigate neuronal loss in neurodevelopmental disease (Schafer et al., 2009). As one would expect, much research examining ENS plasticity has been carried out on the various models of gut perturbation.

Germ-free animal studies of the ENS and implications for synaptic plasticity

GF animals have been used extensively in the search for alterations in ENS plasticity (see **Table 2**). These animals appear to have altered mesenteric nerve firing rates (McVey Neufeld et al., 2015), as well as decreased basal neural excitability, as evidenced by an augmented post action potential, as well as altered intrinsic primary afferent neuron excitability, as measured in the form of an enhanced slow afterhyperpolarization, when compared to SPF and conventionally re-colonized GF control animals (McVey Neufeld et al., 2013). It is now understood that the microbiota plays a crucial role in moderating normal expression of the intracellular calcium-binding protein calbindin (McVey Neufeld et al., 2015). Furthermore, network activity of host physiology in myenteric sensory neurons differed greatly in GF mice from conventional and SPF strains in a study examining jejunum intracellular current-clamp recordings (McVey Neufeld et al., 2013), indicating a fundamental shift in synaptic efficacy in the absence of microbiota. GF animals have been and will continue to be, instrumental in uncovering the fundamentals of ENS mechanisms of plasticity.

Currently, to our knowledge, there are no known studies directly examining ENS physiology utilizing antibiotics but clearly such studies are warranted.

Prebiotic, probiotics and ENS implications for synaptic plasticity

Some of the best links with gut neuroplasticity and microbiome come from studies focused on visceral pain. In a rat model of acute colorectal distension (CRD)-evoked pain, there was an increase in the number of spikes discharged, and a decrease in the threshold for action potential generation, during a standard depolarizing test stimulus. Prior treatment with L. rhamnosus (JB-1) (formally misidentified as a *L. reuteri)*

blocked the CRD-mediated gut electrophysiological changes usually associated with acute visceral pain (Ma et al., 2009), where usually the myenteric intrinsic sensory neurons become hyperexcitable. From an earlier study, (Kamiya et al., 2006) this strain was known to decrease CRD-evoked bradycardia and single unit dorsal root fiber discharge in the anesthetized rat. Direct gastric administration of *L. casei* Shirota strain has been shown to potentially act on the afferent vagal nerve, decreasing sympathetic nerve outflow and regulating tissue-specific efferent sympathetic nervous activity via the CNS (Tanida et al., 2016). It has become apparent that commensal bacteria can signal to local sensory neurons to alter their excitability state, which itself can last long after the bacteria have been removed (Tanida et al., 2005), somewhat reminiscent of hippocampal synaptic plasticity. Even though much advancement has been accomplished examining the effect microbiota-gut-brain perturbations have on neuronal plasticity, and vice versa, much more investigation is still necessary to elucidate this integral and intricate communication pathway.

IX. Factors Influencing the Microbiota-Gut-Brain Axis

There are many factors that have been shown to have a modulating effect on both the brain and microbiota, including socioeconomic status (Bowyer et al., 2019), host diet, congenital factors, environmental factors, exercise and level of host activity, medications and mode of delivery at birth (**Fig. 5**). In the following section, we will delve into the currently known consequences that each of these factors have upon the microbiota-gut-brain axis and consider future possible directions of investigation.

A. Genetics and Epigenetics

The relationship between host genetics and microbiota composition is an important and understudied area of research especially in the context of brain health. There is a growing number of studies examining the relationship between host genetics in humans and mice and the variation of the microbiota and its individual constituent taxa (Bonder et al., 2016). For example, taxa abundance was significantly more correlated in monozygotic twins than in dizygotic twins, with *Christensenellaceae* being the most highly heritable family, while also being associated with low body mass index (BMI) (Goodrich et al., 2014), thus confirming the gut microbiota is an important mediator of the interaction between host-genetics and phenotype (Rothschild et al., 2018; Wang et al., 2018b). Therefore, it may be possible that gut-microbial products could affect neuronal transcription, and hence host behavior (Stilling et al., 2014b). The microbiota may act as an important modulator of the host genome via gene-environment interactions (Stilling et al., 2014a), and in time be recognized as a separate epigenetic entity (Hoban et al., 2018; Stilling et al., 2018).

The microbiota is predominantly in direct contact with epithelial cells, but can also indirectly interact with peripheral neurons and immune cells (Stilling et al., 2014b). In gut epithelial cells, HDAC3 was shown to be critical in maintaining host-commensal signaling (Alenghat et al., 2013). Furthermore, pharmacological inhibition of HDAC activity reversed early-life stress-induced visceral hypersensitivity and anxiety (Moloney et al., 2015), behaviors dependent on appropriate microbiota-gut-brain axis signaling (De Palma et al., 2014; O'Mahony et al., 2011). Future studies should focus on whether bacterial-derived modulators of HDAC activity can modify such physiological and behavioral outcomes.

Another component of genetic-microbiome interactions is at the level of regulatory RNAs or non-coding RNAs which represent a cornerstone of molecular regulation of transcription, gene expression and protein abundance (Ambros, 2001; O'Connor et al., 2016). Animal models of microbial manipulation, including the GF mouse (see **Table 2**), have become invaluable tools in the study of the microbiota-gut-brain axis, and they have been key in studying one branch of the non-coding RNA network, microRNAs (miRNA). miRNAs regulate gene expression through translational repression and inhibition, and they are viable targets for intervention in neuropsychiatric disease (Issler and Chen, 2015; O'Connor et al., 2013; Scott et al., 2015). The gut microbiota has been shown to regulate the expression of microRNA (miRNA) in the amygdala and PFC of GF mice (Hoban et al., 2017). Similarly, depletion of the gut microbiota with an antibiotic cocktail also impacted miRNA expression levels in these specific brain regions. For example, within the amygdala, miR-183-5p was decreased in GF mice, but in recolonized mice, the expression of this miRNA returned to control levels. Also, the hippocampus has demonstrated susceptibility towards gut microbiota diversity and abundance modulation with expression of 7 miRNA's altered in GF mice which were subsequently restored to control levels in re-colonized mice (Chen et al., 2017a).

T. Mode of Delivery at Birth

Mode of delivery has a tremendous impact on the establishment of the microbiota of infants, as the moment of birth is the first opportunity for large-scale bacterial colonization. The initial seeding of microbiota during vaginal-delivery (i.e., natural birth) occurs during parturition, as the infant passes through the birth canal, where they are exposed to the maternal vaginal microbiota. A seminal study has shown that there is vertical transmission of bacteria from the mother to the newborn, with the microbiota of vaginally-delivered babies closely resembling the vaginal microbiota of their mothers (Dominguez-Bello et al., 2010).

On the other hand, when a C-section is performed, vertical transmission of vaginal microbiota from the mother to the baby is circumvented, as the C-section delivered newborn does not pass through the birth canal. Instead, the initial colonization of bacteria in C-section delivered babies seems to be dominated by bacteria typically present on the skin and in the environment, with increased levels of *Staphylococcus* spp. (Dominguez-Bello et al., 2010). Moreover, in that study there was no relation between the specific skin microbiota of the mother and the microbiota of their C-section born infants, demonstrating that bacterial colonization originates from non-maternal sources. In comparison to vaginal delivery, the C-section procedure is associated with decreased colonization rates of *Bifidobacterium*, *Bacteroides* and *Lactobacillus* (Biasucci et al., 2010; Penders et al., 2006), and with a decrease in diversity and richness of the microbiota (Azad et al., 2013; Jakobsson et al., 2014; Stewart et al., 2018). Interestingly, a recent study has shown that in addition to these differences in bacterial representation, mode of delivery has an impact on the fecal virome of infants, with increased viral and bacteriophages diversity in babies born *per vaginum* (McCann et al., 2018).

Despite at least 14 different cohorts showing differences in the microbiota of infants depending on the delivery mode, the full impact of the C-section procedure on the microbiota is still unclear; there are several

confounding factors that can influence the results. Specifically, it has recently been shown that differences in microbiota may be dependent on body site (Chu et al., 2017). Another crucial factor to be taken into consideration is whether the C-section is elective or performed for a medical need, and if so, whether labor was initiated before the C-section procedure. In this case, the microbiota of the C-section born babies seems to be similar to vaginally delivered newborns as these infants come into contact with the birth canal during the early stages of labor (Azad et al., 2013; Chu et al., 2017).

Longitudinal studies have shown that the differences between microbiota attributed to mode of delivery are transitory. Some studies report that birth mode effects on the microbiota can be absent as little as 6-8 weeks after birth (Chu et al., 2017; Hill et al., 2017) or as late as the first two years of life (Bokulich et al., 2016; Jakobsson et al., 2014; Palmer et al., 2007). However, despite this transient nature, early life differential colonization has a long-lasting effect and several studies show a correlation between birth by C-section and increased risk of developing a variety of disorders including obesity, type 1 diabetes, as well as immune disorders such as asthma or allergies (Bisgaard et al., 2011; Blustein et al., 2013; Jakobsson et al., 2014; Montoya-Williams et al., 2018; Roduit et al., 2009). C-section born babies also have a higher risk of developing neonatal infections by methicillin-resistant *Staphylococcus aureus*, (Dominguez-Bello et al., 2010) or *C. difficile* (Penders et al., 2006). Consequently, there appears to be a minor correlation between C-section delivery and poor school performance in adolescents (Curran et al., 2017). In animal models, delivery by C-section leads to transient alterations in the neural development including decreased dendritic arborization (Chiesa et al., 2018; Juarez et al., 2008) and increased neuronal cell death at birth (Castillo-Ruiz et al., 2018). Both neurodevelopmental alterations are associated with early-life changes in vocalization. Further, C-section can also induce long-term changes to dopamine function (Boksa and El-Khodor, 2003).

Independent of the elective or emergency nature of the C-section procedure, more studies are needed to understand the impact of delivery mode and how this impact can be minimized. It has been suggested that using vaginal seeding to transfer vaginal microbiota from the mother to the newborn may be an effective intervention (Dominguez-Bello et al., 2010). Although this technique seems to partially restore the microbiota in these babies, safety concerns have been raised (Cunnington et al., 2016; Stinson et al., 2018) and further studies must be done to evaluate the effects. In addition to this, supplementation with probiotics and prebiotics can be used to decrease the impact of delivery mode on the microbiota (Chua et al., 2017; Moya-Perez et al., 2017a). Factors such as diet (breastfeeding versus formula), environment and antibiotic use also need to be taken into consideration as possible modulators of the microbiome in early-life.

U. Diet

Diet has been shown to be one of the most critical factors modulating gut microbiota composition, and hence the brain and behavior (Turnbaugh et al., 2008). Clinical and preclinical data have shown how different sources of diet significantly affects the composition of the gut microbiota (Sandhu et al., 2017), and mood in non-mood disorder diagnosed individuals (Taylor et al., 2019). Moreover, the effects of diet can be dramatic in terms of both drastic compositional changes and the immediacy of such effects. For instance, individuals

on either an animal- or plant-based diet, when switched to the other diet, experienced substantial changes in the gut microbiota composition, within 24 hours (David et al., 2014). A different dietary pattern has been shown to influence β diversity of the gut microbiota composition, but not α diversity (Basso et al., 2016), which was quite divergent in individuals on an animal-based diet (David et al., 2014). Changes in our lifestyle and food preferences have had a drastic impact on our diet (Aslam et al., 2018; Dinan et al., 2018; Miranda et al., 2016; Moya-Perez et al., 2017a; Reichelt et al., In Press). Indeed, different types of diet have been associated with different impacts on the composition of the gut microbiota. In fact, dietary iron has been shown to regulate insulin resistance to affect susceptibility to infection, highlighting the importance of evolved co-operative mechanisms (Sanchez et al., 2018). However, much more research is needed to delineate if the effects of diets or dietary components on the microbiota are driving changes in overall brain function or happiness or if they are occurring in a microbiota-independent fashion.

Western diet

The Western diet, a diet rich in sugar, salt and/or fat, has been widely regarded as a major contributing factor in the onset of metabolic disorders and associated pathological conditions. Individuals on a Western diet share a similar gut microbiota profile to that observed in obese individuals (David et al., 2014). Intake of an HFD consisting of only animal-based products, including meat and cheese, profoundly shifted their gut microbiota community and altered β diversity, within 48 hours of consumption (Carmody et al., 2015). In another study, five different inbred mouse strains and four different transgenic strains ($Rag^{-/-}$, $MyD88^{-/-}$, NOD2, and ob/ob) crucial for host-microbiota interaction, combined with over two hundred outbred mice, were administered a Western high-fat and high-sugar diet. They reported a dramatic shift in the gut microbiota composition in animal groups due to consumption of the western diet (Carmody et al., 2015).

Further, animal models fed an HFD demonstrated an alteration in their gut microbiota profile with a reduction in *Bacteroidetes* levels and an increase in both *Proteobacteria* and *Firmicute* levels (Hildebrandt et al., 2009). This was also reported in a similar study where the animals fed with a diet rich in animal-derived saturated fats demonstrated a significant increase in *Proteobacteria* (*Bilophila wadsworthia*) abundance (Devkota et al., 2012). It is worth noting that *B. wadsworthia* is a major member of sulfidogenic bacteria found in the human gut and have been shown to induce systemic inflammation (Feng et al., 2017). However, one must consider this increase could be attributed to the source of fat being animal based which is rich in saturated fats and salt. This further illustrates the critical role diet has on gut microbiota function (Wilck et al., 2017) and such strong shifts in gut microbiota profiles are subsequently poised to affect brain and behavior.

Mediterranean diet

The Mediterranean diet has garnered a lot of media attention for its numerous potential health benefits. A Mediterranean diet consists mostly of cereals (whole grains), nuts, legumes, vegetables and fruits with moderate consumption of poultry and fish (Estruch et al., 2013), and results in distinctive and identifiable gut microbiota characteristics (Mitsou et al., 2017). Human intervention studies have shown that the consumption of a Mediterranean diet can dramatically reduce the incidence of neurodegenerative disorders (Karstens

et al., 2019; Romagnolo and Selmin, 2017; Scarmeas et al., 2006), psychiatric conditions, cancer (Schwingshackl et al., 2017) and cardiovascular disease (CVD (Bonaccio et al., 2013; Tsivgoulis et al., 2015; Wu and Sun, 2017)). Interestingly, the Mediterranean diet has been shown in a number of studies to correlate with a reduced risk of depression (Akbaraly et al., 2009; Estruch et al., 2013; Lassale et al., 2018; Milaneschi et al., 2011; Sanchez-Villegas et al., 2006), probably due to the rich source polyphenols present in different components. The positive impacts of a Mediterranean diet are mediated by its anti-inflammatory potential but is also associated with marked changes at the level of the gut microbiota, resulting in an increase in the abundance of *Bacteroides* and *Clostridium* phyla, and a reduction in *Proteobacteria* and *Firmicutes* phyla (Marlow et al., 2013) and associated metabolome (De Filippis et al., 2016). Further, consumption of a Mediterranean or Western diet resulted in distinct mammary gland microbiota and metabolite profiles, with Lactobacillus in greater abundance in Mediterranean diet-fed monkeys, indicating that diet can influence mammary gland microbiota, indicating a potential novel avenue for breast cancer prevention (Shively et al., 2018).

A randomized controlled trial of dietary intervention in major depression (SMILES) confirmed a poor diet correlated with a depressed cohort (N=67) and furthermore showed that the Mediterranean diet intervention (ModiMedDiet) improved depression scores (Jacka et al., 2017). An earlier study in a cohort of 119 depressed patients, which again focused on providing dietary advice, provided some evidence of a beneficial effect of diet to the individual. However, participants in this study were at a mild level of depression at baseline and may have had less scope for improvement (Forsyth et al., 2015).

These studies are just the beginning of a new era of nutritional psychiatry (Jacka, 2017) However, much more work is needed to define what the contribution of the microbiome in mediating such effects is and to determine how diet and its components imbue their effect on the microbiota-gut-brain axis.

Ketogenic diet

The ketogenic diet is a high-fat, low-carbohydrate diet that mimics the metabolic effects of starvation by forcing the body to use its primary fat reserves (Barañano, 2008). It was devised based on the observation that fasting had anti-seizure properties. Administration of the ketogenic diet resulted in increased levels of the ketone bodies β-hydroxybutyrate, acetoacetate, and acetone in the peripheral blood and urine. This elevation in the serum ketones has been shown to inhibit apoptotic proteins and improve mitochondrial activity and thus reducing apoptosis in neurodegenerative diseases (Cavaleri and Bashar, 2018). Moreover, a ketogenic diet mediates its neuroprotective function through the attenuation of oxidative stress and induction of protein expression of antioxidants (Greco et al., 2016), as well as the modulation of neurotransmitter levels such as GABA, monoamines and glutamate (Hartman et al., 2007; Yudkoff et al., 2008). Therefore, a ketogenic diet can offer beneficial health effects towards ameliorating symptoms of neurological conditions including autism, depression, epilepsy, cancer, Alzheimer's and Parkinson's diseases (Bostock et al., 2017; Gasior et al., 2006; Lange et al., 2017). However, more recently the microbiome has emerged as a key player in the mechanism of action of the ketogenic diet.

One study showed the ketogenic diet increasing the relative abundance of *Akkermansia, Parabacteroides, Sutterella and Erysipelotrichaceae* levels in the gut microbiota in mice compared to a control group, and that the gut microbiota is required for ketogenic diet-mediated protection against acute epileptogenic seizures (Olson et al., 2018). Furthermore, colonization of GF mice with ketogenic diet-associated strains, *Akkermansia* and *Parabacteroides,* restored seizure protection. They also reported alterations in colonic luminal, serum, and hippocampal metabolomic profiles that also correlate with seizure protection (Olson et al., 2018). This evidence demonstrates that different dietary components can induce differential effects on the brain via their actions on the gut microbiota. Further studies of the ketogenic diet in animal models of autism (Newell et al., 2016) and schizophrenia (Kraeuter et al., In Press) are also encouraging that such effects extend beyond epilepsy.

Carbohydrates

Carbohydrates contribute to a major portion of the human diet. A culture-based study showed changes in staple carbohydrate acutely altered gut microbiota composition (Li et al., 2017a), in just one week. For instance, wheat and oat-based diets resulted in increases in *B. catenulaturm, B. adolescentis* with a reduction in *Latobacillus*, *Runimococcus* and *Bacteroides*; whereas the consumption of rice suppresses *B. adolescentis and B. longum* levels (Li et al., 2017a).

Carbohydrates come in two forms: digestible and indigestible. Digestible carbohydrates include starch and sugars, which are enzymatically degraded (glucose, fructose, sucrose and lactose) and readily absorbed into the bloodstream and can stimulate insulin release into the bloodstream (Singh et al., 2017). A diet rich in glucose, fructose, and sucrose can significantly increase the abundance of *Bifidobacterium* with a significant reduction in *Bacteroides* (Eid et al., 2014). Mice fed a fructose-rich diet demonstrated significant increases in *Coprococcus, Ruminococcus* and *Clostridium,* and a reduction in *Clostridiaceae* family (Crescenzo et al., 2017). However, various Clostridium cluster species have been shown to be associated with inflammatory bowel syndrome (Bassotti et al., 2018), metabolic disorders (Woting and Blaut, 2016) and psychiatric conditions (Li et al., 2017b).

Undigested carbohydrates i.e. resistant carbohydrates, which are often fermented by the microbiota residing in the distal part of the colon (Sandhu et al., 2017; So et al., 2018), are often a source of microbiota accessible carbohydrates (Joyce and Gahan, 2016), which are a rich carbon source for the microbes and are known to influence the intestinal environment (Lozupone et al., 2012; Sonnenburg and Sonnenburg, 2014). As a result, most prebiotics are undigested carbohydrates known to induce beneficial effects on the host GI system via stimulating the growth of healthy gut microbiota.

Protein

Protein is an important component in our diet as it is the prime source of amino acids, the building blocks of life. Amino acids are critical for the synthesis of neurotransmitters and brain health. There are different

sources of protein based on their origin, such as plant or animal-based protein (Singh et al., 2017). Numerous studies have shown a strong correlation between protein intake and overall microbial diversity (Madsen et al., 2017). Individuals on a plant-based protein diet reported low levels of Firmicutes: Bacteroidetes ratio with higher microbiota diversity compared to individuals on high-fat, high-sugar diet (De Filippo et al., 2010). Different sources of protein in a diet has been shown to influence different gut microbiota profiles (Singh et al., 2017). Rats treated with fish and chicken meat reported a significant increase in *Firmicutes* with a reduction in *Bacteroidetes* abundance in the gut microbiota profile. In contrast, intake of a soy-rich diet resulted in an increase in abundance of *Bacteroidetes* in the microbiota of rats. Furthermore, intake of chicken protein showed an increase in abundance in *Actinobacteria* whereas administration of beef increased the abundance of *Proteobacteria* (Zhu, 2015).

An increase in a protein-based diet has been associated with increases in SCFAs and branched chain amino acids (Singh et al., 2017). For example, consumption of pea protein increases intestinal SCFA levels, which have been associated with anti-inflammatory effects and is critical for the maintenance of the mucosal barrier (Kim et al., 2014). On the contrary, consumption of a protein-rich diet is associated with increases in the abundance of *Bacteroides* because they are crucial for the initial proteolysis of protein into amino acids in the gut. Intake of an animal-based diet showed significant increases in bile-tolerant anaerobes including *Alistipes, Bilophila* and *Bacteroides* (Cotillard et al., 2013; David et al., 2014). A similar effect was observed in a culture-based study comparing Italian children fed animal protein to children from rural Africa fed an agrarian diet; the Italian children showed an increased abundance of *Alistipes* and *Bacteroide*s in their microbiota corresponding to protein intake (De Filippo et al., 2010). Clinical data have shown an increased abundance of *Alistipes* in the gut microbiota of individuals with depression (Jiang et al., 2015). This further supports the role of diet in the modulation of the microbiota-gut-brain axis. Recent research has suggested long-term animal-based diets have a deleterious effect on the gut microbiota (Moreno-Perez et al., 2018). Therefore, more research is required to further dissect the underlying mechanisms of the effect of various components of a protein-based diet on the gut microbiota and its metabolites.

Fats

Diets rich in saturated and trans-fat are associated with a high incidence of CVD and an increase in total blood low-density lipoprotein cholesterol. For example, administration of an HFD to healthy subjects caused a decrease in *Bacteroidete*s levels with an increase in both *Firmicutes* and *Proteobacteria* levels of gut microbiota (Hildebrandt et al., 2009; Zhang et al., 2012a). Similar changes in the phylum were observed with mice fed on a high-fat and high-sucrose diet (Parks et al., 2013).

Healthy fats, also known as polyunsaturated fatty acids (PUFAs), such as omega-6 and omega-3, have been shown to induce beneficial effects by lowering the onset of CVD and can be protective against depression, some cancers, arthritis and cognitive decline (Costantini et al., 2017), as well as to support visual, cognitive, motor, and social development in mice (Carlson et al., 2019). Studies show intake of PUFAs increase the abundance of healthy microbiota including *Roseburia*, *Bifidobacterium* and *Lactobacillus spp*. PUFAs have also been shown to prevent alteration of the gut microbiota (Devillard et al., 2007). For instance, early-life

exposure to omega-3 prevented the onset of metabolic disorders known to be mediated through a perturbed gut microbiota profile post-antibiotic treatment (Kaliannan et al., 2016). Similarly, in adult mice chronic exposure to omega-3 showed a significant increase in *Bifidobacterium* and *Lactobacillus spp.* with higher bifidobacteria to enterobacteria ratio in adult mice exposed to omega-3 (Robertson et al., 2017a). A recent study comparing 876 middle aged female subjects showed that the administration of omega-3 was able to modulate gut microbiota by significantly increasing α diversity (Menni et al., 2017). Docosahexaenoic acid levels from subjects on an omega-3 diet strongly correlated with 38 operational taxonomic units from the *Lachnospiraceae* family (Menni et al., 2017), which have been reported to be in abundance in herbivorous animals (Furet et al., 2009)Bacterial/genetics</keyword><keyword>Feces/*microbiology</keyword><keyword>Humans</keyword><keyword>Polymerase Chain Reaction/*methods</keyword><keyword>RNA, Ribosomal, 16S/genetics</keyword><keyword>Sensitivity and Specificity</keyword><keyword>Sequence Analysis, DNA</keyword></keywords><dates><year>2009</year><pub-dates><date>Jun</date></pub-dates></dates><isbn>1574-6941 (Electronic. In humans, members belonging to the *Lachnospiraceae* family have been shown to be protective against *C. difficle* (Petrof, 2013) and metabolic disorders (Cho et al., 2012). The members of *Lachnospiraceae* are potent producers of SCFAs (Duncan et al., 2002). Overall, more work is needed in understanding the relative contribution of the effects of fats on the microbiota to their impact on brain function.

D. Environment

The environment we live in has perhaps one of the greatest impacts in shaping cross-cultural differences in health outcomes and microbiota composition. For example, different members of the gut microbiota have been shown to be involved in metabolizing more than 40 different environmental chemicals utilizing the enzymes azoreductase, nitroreductase, β-glucuronidases, sulfatases and β-lyases (Claus et al., 2016). Conversely, these chemicals also modulate the gut microbiota composition (Claus et al., 2016), which may thus have effects on brain and behavior through the microbiota-gut-brain axis. For instance, bisphenol A (BPA) is an endocrine-disrupting chemical widely used in the manufacture of plastic containers. Exposure to BPA through diet results in a dramatic reduction in species diversity of gut microbiota in rodents, while increasing the abundance of *Proteobacteria* and *Helicobacteraceae*, and reducing *Clostridia* (Lai et al., 2016).

Heavy metals such as cadmium, mercury, arsenic, and lead are potent toxicants to a living organism (Lu et al., 2014)Inbred C57BL</keyword><keyword>Microbiota/*drug effects</keyword><keyword>Molecular Sequence Data</keyword><keyword>RNA, Ribosomal, 16S/genetics/metabolism</keyword><keyword>Sequence Analysis, DNA</keyword><keyword>Specific Pathogen-Free Organisms</keyword></keywords><dates><year>2014</year><pub-dates><date>Mar</date></pub-dates></dates><isbn>1552-9924 (Electronic; they are highly carcinogenic, can disrupt the immune system, damage nucleic acid structures and cause oxidative stress (Bajaj et al., 2013; Jin et al., 2017; Valko et al., 2006). Exposure to heavy metals can also alter the gut microbiota composition in both animals and humans (Claus et al., 2016; Lu et al., 2014; Zhang et al., 2015). Administration of heavy metals to animals dramatically perturbed their gut microbiota and metabolomic profile, increasing relative levels of *Lactobacillaceae* and *Erysipelotrichaceae* while reducing relative levels of *Lachnospiraceae* (Breton et al., 2013). Low levels of *Lachnospiraceae* have

been associated with human depression (Naseribafrouei et al., 2014)Hedmark University College, Hamar, Norway.</auth-address><titles><title>Correlation between the human fecal microbiota and depression</title><secondary-title>Neurogastroenterol Motil</secondary-title></titles><pages>1155-62</pages><volume>26</volume><number>8</number><edition>2014/06/04</edition><keywords><keyword>Adult</keyword><keyword>Depressive Disorder/*microbiology</keyword><keyword>Feces/*microbiology</keyword><keyword>Female</keyword><keyword>Humans</keyword><keyword>Male</keyword><keyword>*Microbiota</keyword><keyword>Middle Aged</keyword><keyword>RNA, Ribosomal, 16S/genetics</keyword><keyword>16SrRNA gene</keyword><keyword>Illumina deep sequencing</keyword><keyword>depression</keyword><keyword>gut microbiota</keyword></keywords><dates><year>2014</year><pub-dates><date>Aug</date></pub-dates></dates><isbn>1365-2982 (Electronic, hinting at a potential microbiota-gut-brain pathway for the mental health impact of exposure to various environmental pollutants.

Finally, extensive abuse of antibiotic usage by humans has contributed to an increase in the concentration of various antibiotics in our natural environment, including lakes, rivers, agriculture soil, waste and surface water (Dong et al., 2016; Ferro et al., 2016; Qian et al., 2016). In combination with the high levels of antibiotics in many food sources, this will likely have wide-spread consequences not only for individual host health but also from a broader planetary health perspective (Prescott and Logan, 2019).

E. Exercise

Regular exercise is synonymous with good health including brain health. Moderate amounts of exercise can make a meaningful difference to brain structures and their function; for example, in rodents, voluntary exercise impacts the rate of neurogenesis (Adami and Bottai, 2016; van Praag et al., 1999). Exercise has also demonstrated a capacity to overcome age-dependent depletion of hippocampal neurogenesis (van Praag et al., 2005), offering a prospective potential for the reversal of aging within brain structures. Despite the extent of research looking at the relationship between exercise and brain structures/function, there is relatively little information currently available on the effect of exercise on the gut, its microbiota and the influence of exercise upon the gut-brain axis. Exercise along with a number of different factors, such as diet, infection, disease, antibiotics (Grenham et al., 2011; Mackie et al., 1999) also modulates the health and α-diversity of gut microbiota. Moderate levels of exercise are particularly beneficial in reducing levels of stress and building immunity along with positive changes in energy homeostasis and regulation (Bermon et al., 2015; Mika et al., 2015). It is reasonable to think of exercise as being crucial to healthy interactions within the gut microbiota (Choi et al., 2013). The extent of beneficial effects of exercise on the brain via the gut microbiota remains unclear.

Research examining the reciprocal relationship between exercise and gut microbiota composition is still in its infancy, as such little is known about how the gut microbiota may contribute to an individual's exercise performance (Mach and Fuster-Botella, 2017). To date, the majority of studies undertaken have been preclinical animal studies that only indirectly address how exercise positively influences gut microbiota composition. The potential role of exercise-induced microbial changes in preventing HFD induced obesity has been

investigated in mice (Evans et al., 2014). The authors reported that voluntary exercise had significant effects on the relative balance of the major bacterial phyla (*Bacteroidetes and Firmicutes*) that was concurrent with prevention of dietary-induced obesity and normalization in glucose tolerance and that the change in ratio between Firmicutes: Bacteroidetes phyla was proportional to the distance ran (in the HFD fed mice). In a case-control study, free access to exercise was associated with a significant increase *Lactobacillus*, *Bifidobacterium*, and *Blautia coccoides – Eubacterium rectale* species, in principle, improving the α-diversity of the gut microbiota (Queipo-Ortuno et al., 2013), with potential subsequent brain and behavior effects. Exercise was reported to cause massive shifts in mice gut microbiota at nearly the same magnitude as an HFD, with exercise reducing the phyla Bacteroidetes, and increased Firmicutes, Proteobacteria and Actinobacteria. Exercise increased cognitive abilities but was not able to prevent a significant increase in anxiety associated with the HFD. Similarly, the effects of controlled exercise training on gut microbial composition in obese, non-obese, and hypertensive male rats has been studied (Petriz et al., 2014).

Recent human clinical studies have attempted to elucidate how exercise modifies gut microbiota composition using different approaches to stratify the level of physical activity or fitness. In the American Gut Project 1493 participants fecal samples were categorized based on exercise frequency (Never, Rarely, Occasionally (1-2 times per week), Regularly (3-5 times per week) and Daily), and analyses reported that groups who exercised more frequently had a greater α diversity, with an elevation in certain members of the Firmicutes phylum (McFadzean, 2014). A finding along similar lines was reported in a recent study of professional athletes from the Irish international rugby union squad suggested that professional athletes in comparison to the sedentary individuals (Clarke et al., 2014) had a significantly higher diversity of gut microbiota, that positively correlated with protein and creatine kinase consumption, than both control groups matched for physical size, age, and gender. Notably, both the athletes and low BMI group had significantly higher proportions of the genus *Akkermansia* than the high BMI group, a factor generally associated with a healthier metabolic profile (Le Chatelier et al., 2013). Furthermore, indices of microbiota diversity of the athletes positively correlated with protein intake and levels of plasma creatine kinase with support for the protein and microbiota diversity relationship provided by a positive correlation between urea levels - a by-product of diets that are rich in protein and microbiota diversity - suggesting that both diet and exercise are drivers of biodiversity in the gut.

An increase of microbial diversity was once again reported in individuals who performed a 4-day cross-country ski-march in Arctic conditions compared to controls, by (Karl et al., 2017), amongst other changes. To determine whether increasing physical activity and/or increased protein intake modulates gut microbial composition and function, a recent study (Cronin et al., 2018) challenged healthy sedentary adults with an 8-week combined exercise regime, with and without concurrent daily whey protein consumption. A combined aerobic and resistance training exercise regime led to modest alterations in the composition and activity of the gut microbiota of the sedentary individuals. The link of such changes to brain function requires further analysis.

Perhaps the most compelling argument for the benefits of exercise can be taken from studies that show the negative consequences during withdrawal of regular exercise, where symptoms of increased negative mood and fatigue were seen in healthy individuals in as little as 14 days, compared to controls (Kop et al., 2008). It may be that changes in mood and fatigue are associated more with the ability of the gut microbi-

ota to control host tryptophan metabolism and levels of plasma kynurenine, which are strongly correlated with depression (Claes et al., 2011). A recent preclinical study investigated a potential peripheral mechanism through which exercise may bring about its beneficial effects via the kynurenine pathway of tryptophan metabolism and exercise-related PGC-1a1 expression (Agudelo et al., 2014; Harkin, 2014); increased expression of muscle-specific PGC-1a1 in transgenic mice was associated with greater resilience to chronic stress and stress-induced CNS inflammation (Agudelo et al., 2014).

Taken together, although exercise has many potential beneficial effects upon the gut microbiota there is a need for longitudinal studies to resolve the many gaps in current knowledge and to fully understand the mechanisms that regulate changes in the composition and functions of microbiota especially in the context of brain health.

V. Medications and the Microbiome

Among the different therapeutic classes, antibiotics represent the most direct and effective way of targeting the gut microbiota (Antunes et al., 2011; Jakobsson et al., 2010) (see **Table 3**). However, a growing body of evidence suggests that non-antibiotic drugs can also affect the composition of the gut microbiota, with potential implications for behavior, as well as the involvement of the microbiota in drug pharmacokinetics in general (Clarke et al., 2019). In a recent large-scale observational study, the use of medical interventions was associated with a significant variation in the microbiota. Of the 69 microbiota covariates from the Belgian Flemish Gut Flora Project, 13 were drugs belonging to the following classes: antibiotics, osmotic laxatives, IBD medications, female hormones, benzodiazepines, antidepressants, and antihistamines (Falony et al., 2016). In another population-based study, deep-sequencing of the gut microbiotas revealed a relationship between the microbiota and 44 categories of drugs (Zhernakova et al., 2016). As expected, antibiotics were significantly associated with altered microbiota composition; more surprising was the number of other drug categories, including proton pump inhibitors (PPIs), metformin, statins, and laxatives that were also shown to have robust effects on the gut microbiota.

Polypharmacy, the concurrent use of multiple medications by a patient, has also been associated with gut microbiota changes. One study demonstrated that there was a significant negative correlation between the number of different drugs consumed and microbial diversity, although it is unknown if the lower diversity resulted in reduced cognitive function (Ticinesi et al., 2017). Specifically, the drug classes that had the strongest association with single taxa abundance were PPIs, antidepressants and antipsychotics. Gut microbiota samples exposed to different drugs have also been analyzed through metatranscriptomic approaches. The impact of short-term exposure of human feces to various non-antibiotic drugs including cardiac glycosides, a gastric-acid suppressant (nizatidine), an anthelmintic (levamisole), an analgesic (phenacetin), and sulfasalazine, significantly changed the expression of microbial genes linked to drug import and metabolism (Maurice et al., 2013). Several studies have been performed *in vitro* in order to determine the antimicrobial activity of non-antibiotic drugs (Gunics et al., 2002; Gunics et al., 2001; Kruszewska et al., 2000, 2002), all of which have been shown to possess antimicrobial activity, with a strong potential for subsequent functional neural effects.

Given the rise of interest in the microbiota-gut-brain axis, it is unsurprising that in recent years much effort has been placed on understanding the role of psychotropic medications. The antidepressant SSRIs (selective-serotonin reuptake inhibitors), including sertraline, paroxetine and fluoxetine (Jin et al., 2018), have antimicrobial activity against gram-positive bacteria such as *Staphylococcus* and *Enterococcus* (Ayaz et al., 2015; Coban et al., 2009). In addition, the antimicrobial activity of some antidepressants has been confirmed by the synergistic effect of some SSRIs in combination with antibiotics, as well as their effects against some antibiotic-resistant bacteria (Bohnert et al., 2011; Munoz-Bellido et al., 1996, 2000). In one recent study chronic fluoxetine administration induced a depletion of cecal levels of *Prevotella* and *Succinivibrio* (Cussotto et al., In Press), while another witnessed a reduction in *Lactobacillus johnsonii* and *Bacteroidales S24-7* which belong to a phyla that has been associated with the regulation of body mass (Lyte et al., 2019b). Another class of antidepressants, tricyclic antidepressants (TCAs), have been shown to prevent the growth of gut pathogens such as *E. coli*, *Yersinia enterocolitica* (Csiszar and Molnar, 1992; Molnar, 1988) and the parasite Giardia lamblia (Weinbach et al., 1992).

Antipsychotics belonging to the non-antibiotic phenothiazines class and their derivatives have been shown to protect mice from *E.coli* infection (Komatsu et al., 1997). This action has been confirmed in a clinical study where promethazine was shown to exert a synergistic effect when combined with gentamycin in children with frequently recurring pyelonephritis (Molnar et al., 1990). In a large cohort study in elderly hospitalized patients, antipsychotics were one of the three drug classes that exhibited the strongest association with single taxa abundance, together with PPIs and antidepressants (Ticinesi et al., 2017). Another recent study of patients with bipolar disease found that atypical antipsychotics induced a decrease in microbial diversity, with the effect being present in females but not in males (Flowers et al., 2017). At the microbiota genus level, individuals in this bipolar cohort treated with atypical antipsychotics exhibited a significant increase in *Lachnospiraceae* abundance and a significant decrease in *Akkermansia*. Finally, in the large-scale study of > 1000 drugs mentioned above nearly all subclasses of the chemically diverse antipsychotics exhibited anticommensal activity (Maier et al., 2018), raising the possibility that direct bacterial effects might be part of the mechanism of action of these drugs. This is in line with animal studies on antipsychotics whereby chronic administration of olanzapine and risperidone affects the gut microbiota composition (Davey et al., 2013; Davey et al., 2012; Kao et al., 2018; Morgan et al., 2014). Overall, one cannot neglect the pressing need to examine any potential effect all orally consumed medications may have on our microbiota, and subsequent efficacy of the active compounds thereafter.

W. Stress

Stress is a state in which the normal homeostasis of an organism is disturbed due to an actual or perceived threat (de Kloet et al., 1994; McEwen et al., 2016). Acute stress activates the HPA axis (see **Section IV. J**), resulting in an immediate release of cortisol (or corticosterone in rodents; (Dickerson and Kemeny, 2004; Smith and Vale, 2006)). This is an evolutionarily conserved response that prepares the individual to defend against or escape from threat. After the threat subsides, normal homeostasis should return. However, when that fails to occur chronic activation of the stress response results in dysregulation of the HPA axis (Dickerson and Kemeny, 2004) and an increased risk of subsequent maladies. In humans, stress-related disorders such

as anxiety and depression cost the European Union upward of €160 million in 2010 (Olesen et al., 2012). As such, chronic stress is rapidly becoming a global societal challenge.

More than four decades ago, a link between stress and the abundance of lactobacilli in mice was discovered for the first time (Tannock and Savage, 1974). This finding was subsequently replicated in the rhesus monkey (Bailey and Coe, 1999), or rat models of early life maternal separation stress (Gareau et al., 2007; O'Mahony et al., 2011; Rincel et al., 2019). Many preclinical studies have since demonstrated that stress impacts gut microbial composition in a number of different hosts, including rodents (Bharwani et al., 2016; Golubeva et al., 2015; Partrick et al., 2018), pigs (Mudd et al., 2016), horses (Mach and Fuster-Botella, 2017) and non-human primates (Bailey and Coe, 1999; Bailey et al., 2004) (see **Table 1**). In one instance, chronic psychosocial stress induced an increase of *Helicobacter pylori* in the gastric mucosa, concurrent with an increase in serum corticosterone levels in mice (Guo et al., 2009). These effects appear to be replicated across different stress models. Psychological stressors ranging from water avoidance to maternal separation, heat and acoustic stress and overcrowding have all been shown to change the composition of the gut microbiota (Bailey et al., 2011; Bharwani et al., 2016; De Palma et al., 2015; Hsiao et al., 2013; O'Mahony et al., 2009; Sun et al., 2013). In addition, maternal stress during pregnancy display a distinct fecal microbiota profile (Hantsoo et al., 2019; Hechler et al., 2019), that has generational consequences. The maternal microbiota influences offspring microbiota and correlates with hyper-reactivity of the HPA axis, together with other perinatal factors, as a key determinant of offspring outcomes (see **Section III. A).** Furthermore, the transfer of the maternal vaginal microbiota from stressed dams to non-stressed pups is sufficient to alter their response to stress in adulthood (Jasarevic et al., 2018). These findings also translated to humans in a population-based study whereby infants born to mothers with high cumulative stress during pregnancy exhibited an aberrant microbial composition (Zijlmans et al., 2015). It has become quite clear that many factors one comes in contact with daily can have an impact on our microbiota-gut-brain axis, some as subtle as food cravings to as long-lasting and impacting as congenital heredity and mode of delivery. In the following section (see **Section VII**), we will delve further into behaviors modified directly and indirectly by the microbiota, after which we will examine the role of the microbiota-gut-brain axis in disease.

X. Circadian Rhythm

The circadian rhythm describes the 24-hour cycle that regulates bodily functions, from rest/wake timing to cellular level metabolic processes in the majority of organisms, including humans, mice, and bacteria (Voigt et al., 2016a). Modern day lifestyles contain many unavoidable and harmful disruptions to the circadian rhythm including jet lag and shift work. Both have been linked to metabolic (Arble et al., 2010; Maury et al., 2010) and psychiatric (Pantazopoulos et al., 2018; Wulff et al., 2010) illness. Recently, the interplay between circadian rhythm and the microbiome is being investigated in the context of obesity, CVD, diabetes, psychiatric disorders, and neurodegenerative disorders (Dyar et al., 2018; Liang and FitzGerald, 2017; Voigt et al., 2016a) which may have key implications for our understanding of the microbiota-gut-brain axis.

The mammalian circadian clock follows a feedback loop of transcription and translation. The positive transcription factors *CLOCK* and *BMAL1* regulate expression of the inhibitory transcription factors Period (*PER1/2*)

and cryptochrome (*CRY1/2*), which in turn repress *CLOCK* and *BMAL1,* restarting the cycle (Takahashi, 2017). Interestingly, the average human circadian rhythm is 24.2 hours which is amenable to the endogenous biological clock *zeitgebers,* light and food (Voigt et al., 2016a). Recent evidence has identified the microbiota as a potential circadian clock modulator, effecting change to the peripheral and central clocks (Liang and FitzGerald, 2017; Thaiss et al., 2014). Furthermore, it appears that circadian disruption can alter the intestinal microbiota (Voigt et al., 2014). When there is a change in the light, food (diet), or the microbiome, the peripheral clocks are affected. Further, disruption or dysregulation of the peripheral or central clocks can lead to serious negative consequences, including microbiome dysregulation, as one recent study has demonstrated utilizing transgenic mice containing deletions of circadian clock genes (Voigt et al., 2014). The researchers witnessed significant changes to the microbiome, and a dampening or abolishment of microbiota compositional oscillations (Liang et al., 2015b; Thaiss et al., 2014; Voigt et al., 2016b). In one study in particular, the dysregulation of the microbiota was rescued by specifically timed feeding (Thaiss et al., 2014). From a human perspective, it has been reported that patients with IBD have an overall reduction in circadian clock gene transcripts (Hill-Burns et al., 2017a). Since both circadian disruption and microbiome dysregulation express complex bidirectional regulation leading to immune activation and inflammation, it may be that inflammation acts as an intermediary between the circadian rhythm and the microbiome (Hill-Burns et al., 2017a; Voigt et al., 2016a). The mammalian circadian clock may be modulated by the microbiome by tuning the amplitude of the circadian gene NFIL3 with the microbial metabolite LPS, potentially resulting in microbially controlled energy storage and body-fat accumulation (Wang et al., 2017)

Upon examination of circadian clock mRNA in GF mice, it was reported that the microbiota was required for correct integration of liver clock-oscillations, which in turn regulate metabolic gene expression for optimal liver function (Montagner et al., 2016). Moreover, conventional mice treated with antibiotics demonstrated systemic disruption of microbiota diurnal rhythmicity (Thaiss et al., 2016). Indeed, host homeostatic colonization disruption leads to a loss in microbiota compositional and biogeographical rhythmicity, which in turn disrupts hosts rhythmicity (Thaiss et al., 2016). Further, a human study examining jet lag and mouse models of shift work found an arrhythmic microbiome that had a significantly altered microbiota composition that promoted metabolic imbalance, which was transferrable to GF mice via FMT (Thaiss et al., 2014). A contemporaneous study reported that mice undergoing a 12-hour phase shift, mimicking human shift work when fed a high-fat and high-sugar diet, experienced a significant decrease in microbial diversity and marked changes to their microbiota (Voigt et al., 2014). The exacerbation of shift work and jet lag's adverse metabolic effects by a high-fat diet, or a high-fat and high-sugar diet, is especially poignant considering these lifestyles are often accompanied by poor eating habits, and the microbiota modulation presents as a potential therapeutic avenue for these conditions. More work is needed to understand the relationship between circadian rhythms, microbiota and brain health but it is clear that inter-relationship will be physiological and perhaps clinically relevant.

X. Behavior and the Microbiota-Gut-Brain Axis

The microbiota-gut-brain axis is poised to affect and be reciprocally affected by many factors, including social and cognitive behavior, fear, stress and food intake (Fig. 6.) We are slowly beginning to understand the rela-

tive contribution this axis has to such complex physiology and behavior. In this section, we will examine these behaviors and propose possible therapeutic avenues.

A. **Food Intake**

What we eat and when we eat is likely affected by the composition and function of our microbiota, where an array of orexigenic (i.e., ghrelin, NPY) and anorexigenic hormones (i.e., GLP-1, PYY, CCK, and CRF; see **Section VII D and F**) play a crucial role (Fetissov, 2017; van de Wouw et al., 2017). This is supported by the fact that many conditions wherein food intake behavior is dysregulated, like anorexia nervosa and obesity (see **Section XI J**), are associated with an altered gut microbiota (Kleiman et al., 2015; Le Chatelier et al., 2013; Mack et al., 2016; Morita et al., 2015; Turnbaugh et al., 2008; Turnbaugh et al., 2006; Turnbaugh et al., 2009). In addition, amelioration of obesity by bariatric or Roux-en-Y gastric bypass surgery results in a change in gut microbial composition (Gralka et al., 2015; Tremaroli et al., 2015; Zhang et al., 2009), even though this is not the case for weight gain in anorexia nervosa (Mack et al., 2016). Many conditions in which food intake behavior is dysfunctional share co-morbidities with other psychiatric disorders (Klump et al., 2009; Lopresti and Drummond, 2013). As such, it is important to note that levels of depression, anxiety, and eating disorder psychopathology correlate with various measures of gut microbiota composition (Kleiman et al., 2015).

One of the most provocative propositions has been that gut microbes are under a selective and evolutionary pressure to manipulate the eating behavior of the host to enhance their own fitness, which can be done by inducing dysphoria until we consume the nutrient these microbes thrive on, or by generating cravings for food that specifically promote their own growth and survival (Alcock et al., 2014). Gut microbial diversity plays a key role in this theory, as decreased diversity inherently has an increased prevalence of specific bacterial species, which might allow them to affect the host more efficiently. This is because these microbes have relatively less competition and have to spend fewer resources on survival while having more resources available for the manipulation of host eating behavior (Alcock et al., 2014). Such theories are difficult to prove experimentally. However, an intriguing study in Drosophila points to a key role for the microbiota in food choice behavior, as when GF flies were given *Acetobacter pomorum* and *Lactobacillus spp.,* it changed their overall food preference (Leitao-Goncalves et al., 2017).

Various mechanisms through which the microbiota can affect food intake behavior have been suggested. Gut microbes can produce protein sequences of ≥5 amino acids that share an arrangement identical to various appetite-regulating peptides in the host (Ericson et al., 2015; Fetissov et al., 2008), which could trigger the production of immunoglobulins. These immunoglobulins can inhibit the degradation of such hormones, which has been reported for the orexigenic hormone ghrelin (Takagi et al., 2013). As mentioned earlier (**Section VII. D**.), E. coli has been reported to produce caseinolytic protease B (ClpB), a small protein sequence and antigen-mimetic of α-MSH (Breton et al., 2016a; Tennoune et al., 2014; Tennoune et al., 2015). Increased ClpB levels have been reported in anorexia nervosa, bulimia nervosa, and binge-eating disorder and were correlated with various psychopathologic traits (Breton et al., 2016a). Administration of ClpB-producing E. coli decreases short-term body weight and food intake compared to ClpB-deficient E. coli (Tennoune et al., 2014). As such, gut microbial-derived peptide sequences provide a pathway in which the gut microbiota can

influence host-eating behaviors.

Another likely mechanism by which the microbiota can influence food intake behavior is by affecting the ability to sense and taste nutrients. Interestingly, obesity is associated with a decreased responsiveness to sweet and fatty tastes, which results in needing a higher intensity of such stimuli to attain the same level of taste perception (Berthoud and Zheng, 2012). Anorexia nervosa is also associated with an impaired taste perception (Dazzi et al., 2013; Szalay et al., 2010), and weight gain has been shown to ameliorate these impairments (Aschenbrenner et al., 2008; Nozoe et al., 1996). Signals conveying taste are mediated through taste receptors on the tongue, which can be either transmitted directly through the solitary tract to the thalamus (Breslin and Huang, 2006; Rolls, 2015), or by the local secretion of anorexic hormones like GLP-1, PYY and CCK (Feng et al., 2008; Martin et al., 2009; Shen et al., 2005). The role of these anorexigenic hormones is supported by the fact that PYY transgenic mice have a decreased behavioral response to fat- and bitter-tasting compounds, of which their response to fat-taste is improved after reconstitution of salivary PYY (La Sala et al., 2013). A continuous supply of oral taste receptor cells plays a crucial role in this process, and the disruption hereof can be detrimental for taste signaling (Feng et al., 2014). Particularly the immune system is implicated in taste receptor cell renewal, as its activation results in the decrease of cell renewal and lifespan (Cohn et al., 2010; Kim et al., 2012; Wang et al., 2007). Moreover, systemically administered LPS results in decreased taste cell lifespan (Cohn et al., 2010), as well as decreased taste preference (Aubert and Dantzer, 2005; Cross-Mellor et al., 2005; Larson, 2006), indicating systemic immunity additionally plays a role in taste perception. Overall, data indicate that the GI microbiota can affect taste perception, although more studies on microbiota-dependent mechanisms need to be performed to further validate this theory.

B. **Social Behavior**

Sociability may be classified as any form of interaction between more than one animal. It is a fundamental behavior for all species as it facilitates many beneficial outcomes such as learning, cooperation, protection, and mating. Interestingly, social behavior across the animal kingdom appears to be strongly influenced by the microbiota. Studies in GF mice showed they spend less time interacting with a novel conspecific compared with a conventionally colonized mouse (Buffington et al., 2016; Desbonnet et al., 2014; Sgritta et al., 2019; Stilling et al., 2018), but see (Arentsen et al., 2017). Moreover, while a conventionally colonized mouse will prefer to spend more time interacting with a novel conspecific over a familiar one, GF mice are unable to distinguish between either animal, which represents a cognitive deficit in the identification of social novelty (Desbonnet et al., 2014; Stilling et al., 2018). These findings of social deficits in the absence of a microbiota have been corroborated with studies of antibiotic administration in rodents. Several studies have documented that antibiotic administration, resulting in a marked reduction in gut microbial diversity, is associated with deficits in social behavior (Degroote et al., 2016; Desbonnet et al., 2015). The precise mechanisms that underlie microbiota-mediated regulation of social behavior are unknown and most likely involves a multitude of biological pathways acting cooperatively.

However, several studies have taken great strides in elucidating how gut bacteria may influence social behaviors. For instance, knockdown of Pglyrp2 in mice resulted in a greater level of social interaction with conspecifics, which suggests that bacterial components such as peptidoglycan are capable of crossing from the gut into the brain (see **Section IV. K.) and** influencing social behavior circuitry via this signaling cascade (Arentsen et al., 2017). The amygdala appears to be a brain region that is central to the influence of the microbiota on social behavior. GF mice display heightened expression of transcription factors related to neuronal activation (e.g., fos) in the amygdala relative to conventional controls (Stilling et al., 2015). Moreover, morphological analysis of the murine GF amygdala reveals extensive neuronal hypertrophy and dendritic arborization leading to an overall increase in the volume of the various amygdalar sub-nuclei (Luczynski et al., 2016a). In response to social interaction, there are profound alterations in the transcriptome and spliceosome in the amygdala of GF mice, which may contribute to the social deficits observed (Stilling et al., 2018). These genetic and functional changes in the amygdala of GF mice demonstrate that this brain region is not only a crucial node in the neuronal circuitry underlying social behavior, but it is also the focal point through which the microbiota modulates this behavior.

As the microbiota appears to be an influential factor in shaping social behavior, it stands to reason that modulation of the microbiota through diet or probiotic administration can also affect sociability. Indeed, administration of *L. reuteri,* to mice resulted in an increase in the circulation levels and expression of oxytocin, which was associated with an increase in social behavior (Buffington et al., 2016; Poutahidis et al., 2013). In another experimental rodent model, bile duct ligation-induced social withdrawal behavior in mice was ameliorated following treatment with the probiotic mixture, VSL#3, in addition to lowering circulating levels of proinflammatory cytokines (i.e., TNF-***α***) (D'Mello et al., 2015). Consequently, modulation of immune signaling to the brain may also be an additional means through which the microbiota may influence social behavior. Dietary mediated alterations in the microbiome may also have an important bearing upon neurocircuitry of social behaviors, especially during development. Experimental dietary deficiency in polyunsaturated omega-3 fatty acids resulted in social behavior impairments in adult, but not adolescent, rats (Robertson et al., 2017a). Moreover, supplementation of mice with omega-3 fatty acids prevented social behavior impairments following induction of allergy (de Theije et al., 2014a). While a polyunsaturated fatty acid-rich diet may be exerting its prosocial effects via modulation of fatty acid membrane levels in the brain, it has also been shown to positively affect the composition of the microbiota (Pusceddu et al., 2015; Robertson et al., 2017b) and thus a role for the microbiota is likely (Robertson et al., 2018). Future studies should focus on translating these animal studies to the human disorders of social behavior such as ASD, schizophrenia and social anxiety disorder.

C. Cognition

There is increasing evidence supporting the idea that changes in the composition of the gut microbiota can influence cognitive function at multiple levels.

Rodent Studies

The complete absence of microorganisms can induce numerous disruptions of host cognition. It has been shown that GF mice exhibit an impaired ability to remember a familiar object when presented with a novel

object (Gareau et al., 2011; Luk et al., 2018), as well as impaired working memory in remembering a familiar environment in the spontaneous alternation task (Gareau et al., 2011). In addition, these animals exhibit altered BDNF expression in the hippocampus (Bercik et al., 2011a; Diaz Heijtz et al., 2011; Gareau et al., 2011), which as stated earlier has an important role in synaptic plasticity and cognition (Baj et al., 2013; Lu et al., 2014; Neufeld et al., 2011), suggesting a crucial involvement of microbes in regulating hippocampal-dependent memory function.

Antibiotics are known to disrupt the intestinal microbial community, which can result in detrimental effects on brain function and behavior (see **Table 3**). It has been shown that antibiotic administration from weaning age and onwards can induce gut microbiota changes, along with subsequent object recognition memory impairments and altered BDNF expression in the hippocampus when measured during adulthood (Desbonnet et al., 2015). More recent studies have found similar impairments in object recognition memory after the administration of antibiotics in adulthood. An 11-day exposure to an antibiotic cocktail disrupted object recognition memory in adult male mice (Frohlich et al., 2016). This memory impairment was associated with changes in the expression of signaling molecules relevant to cognition (i.e., BDNF, GRIN2B, 5-HT transporter and neuropeptide Y) within the hippocampus among other memory-related brain regions. Similarly, chronic long-term antibiotic treatment was found to induce similar memory deficits in adult female mice (Mohle et al., 2016), along with decreased hippocampal neurogenesis.

Such findings highlight the importance of the gut microbiota in recognition memory performance and hippocampal function. Nonetheless, antibiotic-induced microbiota depletion has generated mixed results in other types of hippocampal-dependent memories. While chronic antibiotic treatment impaired spatial memory in the Morris Water Maze in adult rats (Hoban et al., 2016a; Wang et al., 2015) acute treatments did not affect this type of memory when administered in early life in rats (O'Mahony et al., 2014), nor when administered during adulthood in mice and tested in the Barnes maze (Frohlich et al., 2016). This suggests differential effects based on rodent background, behavioral task, and especially in the type and/or duration of antibiotic treatment. Hence, further research is needed to clarify the effects of gut microbiota depletion on spatial memory.

A large number of studies have focused on exploring the beneficial effects of probiotic and prebiotic treatments in modulating health and preventing or restoring cognitive deficits associated with changes in gut microbiota (see **Table's 4** and **5**). In this regard, Lactobacillus strains have been widely used for this purpose. Indeed, different Lactobacillus strains were capable of restoring deficits in object recognition memory induced by chronic restraint stress (Liang et al., 2015a), as well as preventing these deficits in GF mice (Gareau et al., 2011), in a mouse model of colitis (Emge et al., 2016), and in immunodeficient mice (Smith et al., 2014). These strains also proved effective in restoring spatial memory impairments induced by diet in immunodeficient mice (Ohland et al., 2013), age (Jeong et al., 2015), hyperammonemia (Luo et al., 2014), and by gut microbiota depletion after chronic antibiotic treatment (Wang et al., 2015). It has been found that probiotic treatment with selective Bifidobacterium strains in healthy mice can selectively improve object recognition memory, decrease the number of errors in a spatial memory test, and induce better long-term learning in

fear conditioning (Savignac et al., 2014) indicating the beneficial effects of a rich microbiota in cognitive behavior. Furthermore, a recent study found a pro-cognitive effect of the prebiotic B-GOS® in healthy rats (Gronier et al., 2018). B-GOS® fed rats showed an improved performance in the attentional set-shifting task, thereby indicating greater cognitive flexibility, along with an increase in cortical NMDAR function within the frontal cortex.

Other probiotic strains were able to induce similar beneficial effects. For example, probiotic supplementation with a mixture of Lactobacillus and Bifidobacterium strains considerably improved spatial memory deficits in diabetic animals (Davari et al., 2013). VSL#3, a commercially available probiotic mixture consisting of Streptococcus, Bifidobacterium and Lactobacillus strains restored object recognition memory impairment induced by chronic antibiotic treatment (Mohle et al., 2016), and cafeteria-diet supplementation (Beilharz et al., 2018). More recently, a mixture of 'infant type' Bifidobacterium strains had the same beneficial effects improving the cognitive deficits in GF mice (Luk et al., 2018), suggesting the importance of early-life microbiota in adult cognitive behavior. Together, these data demonstrate the substantial impact of enriching the gut microbiota in reverting cognitive deficits associated with diverse factors.

Human Studies

Although there is abundant evidence from animal research supporting the role of the gut microbiota in modulating cognitive function, only a few studies have examined the influence of gut microbes on human cognition. Most of these studies are relatively small, but some are promising nonetheless. One of these studies showed that the gut microbiota composition of obese and non-obese subjects was linked with scores in speed, attention, and cognitive flexibility in a Trail Making Test coupled with alterations in neural activity in the thalamus, hypothalamus, and amygdala, suggesting that obesity affects the microbiota composition and subsequent cognitive performance (Fernandez-Real et al., 2015). In a more recent study, the microbiota composition in one-year-old babies was associated with cognitive development tested with the Mullen Scales of Early Learning showing differences in brain volume (Carlson et al., 2018). They identified three groups depending on the microbial composition (i.e., high levels of Faecalibacterium, Bacteroides, and Ruminococcaceae), and found better performance in the group with higher levels of Bacteroides. This group was also less likely to be born via C-section, which fits with previous studies linking mode of delivery with child cognitive development (Polidano et al., 2017), highlighting the importance of gut microbiota colonization in cognitive development and function.

Probiotics have also been employed in humans demonstrating beneficial effects on cognitive performance in both healthy and diseased individuals. Treatment with Lactobacillus strains in healthy elderly subjects induced an improvement in cognitive test performance compared to a placebo group (Chung et al., 2014). In healthy women, consumption of a fermented milk product supplemented with a probiotic modulated the activity in brain regions involved in cognitive performance during an emotional attention test (Tillisch et al., 2013). Improvements in memory tasks and subjective improvements in mood were observed in a study on healthy individuals receiving a prebiotic of oligofructose-enriched inulin (Smith et al., 2015). *B. longum* 1714 which had shown pro-cognitive effects in mice (Savignac et al., 2014) was shown to attenuate stress-in-

duced cortisol increases reducing perceived and subjective anxiety, and moderately enhancing hippocampus-dependent visuospatial memory performance (Allen et al., 2016). Moreover, *L. plantarum* P8 was also found to alleviate stress and anxiety while reducing levels of pro-inflammatory cytokines in stressed adults, accompanied by enhanced social-emotional cognition and verbal learning and memory (Lew et al., 2018). Recently, a probiotic mixture containing *B. longum* and different *Lactobacillus* strains positively affected cognitive function and metabolic status in Alzheimer's disease patients (Akbari et al., 2016). Further, cognitive improvements in impulsive choice and decision-making were observed in patients diagnosed with Fibromyalgia after receiving a multispecies probiotic intervention (Roman et al., 2018), a group of patients that present with an altered microbiome as measured by disrupted microbiota metabolites (Malatji et al., 2019). These results taken together indicate the potential efficacy of probiotics for improving cognitive function in both healthy and AD clinical populations. However, much more work is needed to understand why specific strains/interventions have the potential to modulate cognition and the constraints that exist on this. Moreover, it is clear that the combination of brain imaging techniques with neuropsychological and cognitive measures will greatly enhance our understanding of the microbiota-gut-brain axis in regulating cognition in healthy and vulnerable populations.

D. Fear

One aspect of cognition that warrants deeper examination is that of fear regulation. Exaggerated fear is a core symptom of clinical anxiety and fear responding is closely linked to stress (Maren and Holmes, 2016; McEwen et al., 2016; Raio and Phelps, 2015), which (**as described in Sections VI. G. and VII. H**.) is tightly intertwined with gut-brain axis function. The expression and inhibition of learned fear is largely regulated by the amygdala, hippocampus, and PFC in adult rodents and humans (Knapska et al., 2012; LeDoux, 2003; Maren and Quirk, 2004; Tovote et al., 2015) and these brain regions are all modulated by changes in the microbiota (Bercik et al., 2011a; Clarke et al., 2013; Cowan et al., 2018; Gacias et al., 2016; Hoban et al., 2017; Hoban et al., 2016b; Luczynski et al., 2016b; Neufeld et al., 2011; Ogbonnaya et al., 2015; Stilling et al., 2015). Despite this, studies of the microbiota in fear regulation remain relatively scarce.

In humans, there are now a few fMRI studies linking the gut microbiota to functional brain activity during observation of threat stimuli (negatively valanced emotional images). The initial study in this area demonstrated, in a sample of healthy women, that intake of a fermented milk product containing multiple probiotic strains could reduce the neural response to faces showing negative affect (fear or anger) (Tillisch et al., 2013). Specifically, brain reactivity was reduced across a distributed network of brain regions including the PFC and parahippocampal gyrus. Another study from the same group later showed that natural differences in the microbiota composition of healthy women were associated with altered reactivity of the right hippocampus to negative emotional images (Tillisch et al., 2017). Finally, in a recent study of adversity-exposed, and control children, variation in Bacteroides and Lachnospiraceae were associated with brain reactivity to fear faces, particularly in the PFC (Callaghan et al., 2019).

Using animal models, emerging research is beginning to delineate the links between the microbiota and

learned fear responses, or more specifically fear memory and extinction. With GF mice, short-term fear recall was shown to be impaired in the absence of the microbiota (Hoban et al., 2018). Adult conventionally-colonized, GF, and ex-GF mice underwent classical fear conditioning, whereby a previously innocuous conditioned stimulus was paired with an innately aversive unconditioned stimulus. Six hours later, GF animals exhibited low levels of conditioned fear responding relative to conventionally-colonized animals, but this deficit was rescued in the ex-GF mice that were re-colonized at weaning. These behavioral changes were accompanied by altered amygdala gene expression, specifically indicating elevated baseline amygdala activity and reduced responsiveness to the fear stimuli in the GF animals. Similar impairments of fear recall and additional enhancements of fear extinction are observed following acute antibiotic exposure in humans and rodents (Bach et al., 2018; Davis et al., 2006; Rodrigues et al., 2014). Although the broad-spectrum antibiotics used in these cases (doxycycline and D-cycloserine) were chosen for their direct neuromodulatory properties, the similarities to GF function suggest that it is worthwhile considering the possibility of an alternate microbiota-mediated mechanism in these cases as well.

Providing further support for microbial modulation of learned fear, fear responding is also altered by probiotic treatments, at least in rodents. These effects are strain-dependent, with different outcomes depending on the chosen probiotic. For example, *B. longum* 1714 enhanced fear learning and short-term memory in adult mice, without affecting extinction, while *B. breve* 1205 had no effect on either measure (Savignac et al., 2015). Another probiotic strain, *L. rhamnosus* (JB-1), slowed extinction learning in adult mice (Bravo et al., 2011), whereas heat-killed *Mycobacterium vaccae* has the opposite effect, accelerating extinction learning in adult rats (Fox et al., 2017). Finally, administration of a probiotic formulation containing *L. rhamnosus* R0011 and *L. helveticus* R0052 has been shown to prevent the effects of early-life stress on fear behavior and its supporting neural network during development (Callaghan et al., 2016; Cowan et al., 2016). Specifically, young rats exposed to early-life stress exhibit a phenotype characterized by persistent fear memory and high rates of fear relapse following extinction (Callaghan and Richardson, 2013; Cowan et al., 2013), a profile that is passed down the male line for at least two generations (i.e., the grand-offspring of the stressed males exhibit the same high-fear phenotype despite never directly experiencing stress) (Callaghan et al., 2016). Probiotic treatment rescued the normal trajectory of fear memory development in stressed rats, restoring an age-appropriate normal phenotype of rapid forgetting and low rates of fear relapse not only in probiotic-exposed neonatal rats but also their offspring (Callaghan and Richardson, 2013; Cowan et al., 2013).

E. Stress-Related Behaviors

As described previously (see **Section VI. G**.), an ever-growing body of preclinical studies using a variety of animal models has shown that stress can alter the gut microbiota (see **Tables 2-5**). This relationship, like the microbiota-gut-brain axis itself, is bidirectional – the microbiota can modulate stress-induced alterations in anxiety, memory, cognition and neuroinflammation (for reviews, see Cussotto et al., 2018; Farzi et al., 2018; Foster et al., 2017; Rea et al., 2016; Sherwin et al., 2016a). Many studies were conducted using GF mice (see also **Section II. A.** and **Table 2**) (Clarke et al., 2013; Crumeyrolle-Arias et al., 2014; Diaz Heijtz et al., 2011; Luczynski et al., 2016a; Neufeld et al., 2011; Sudo et al., 2004). Their collective findings were critical in shedding light on the existence of a link between the microbiota and stress. Moreover, this work paved the way

for further research on the stress-microbiota link to explore potential therapeutic benefits for microbiota manipulations in the context of stress.

Stress Susceptibility

Given the link between the microbiota and the stress response, a relationship between resilience and microbiota composition has also been proposed (Kentner et al., 2018). Current studies are exploring whether basal microbiota composition itself can predict stress susceptibility. For example, a single exposure to social stress in Syrian hamsters was sufficient to induce changes in the microbiota, where multiple encounters exacerbated the effect (Partrick et al., 2018). Microbiota was differentially affected depending on the outcome of the chronic social defeat encounter. Further, using a chronic social defeat stress protocol, mice with higher social avoidance scores had greater correlational changes in cecal microbiota taxa than controls (Szyszkowicz et al., 2017). When analyzing the fecal microbiome from rats more vulnerable to repeated social defeat stress, compared to those classified as more resilient, shotgun metagenome sequencing identified an increase in the expression of immune-modulating microbiota, including *Clostridia*, in the vulnerable rats (Pearson-Leary et al., 2019). The depressive-like behavioral phenotype was transferrable via FMT from stress vulnerable to naïve rats, where ventral hippocampal microglial density and IL-1β expression were enhanced, when compared to naïve rats receiving FMT from stress resilient donors (Pearson-Leary et al., 2019). In a different study, defeated mice displayed increased depressive-like behaviors that correlated with a reduction in the abundance of specific bacterial genera (McGaughey et al., 2019). Future studies should focus on whether the microbiota provides a mechanism for stress susceptibility or resilience in both rodents and humans.

Probiotics and stress-related changes

There is growing evidence that specific manipulations of the microbiota might modulate the negative effects of stress, including stress-related behavior and HPA axis activation (Sarkar et al., 2016). Much of this work has focused on administration of probiotics, and particularly *Bifidobacterium* and *Lactobacillus* species, with promising effects observed on stress and related anxiety and depression in both preclinical and human studies (**see also Sections VIII:E & VIII:F and Table 5**) (Butel, 2014; Pirbaglou et al., 2016; Wallace and Milev, 2017).

In a randomized placebo-controlled fMRI study, a multispecies probiotic increased a buffer against stress-related negative effects on working memory, specifically in PFC recruitment, identifying the use of probiotics as a support for cognition under stressful situations in healthy individuals (Papalini et al., 2019). In a preclinical study, oral administration of *L. rhamnosus* (JB-1) reduced stress-induced corticosterone responses as well as anxiety- and depression-related behavior in mice, effects that were prevented by vagotomy (Bravo et al., 2011). Further, *L. farciminis* prevented hyper-activation of the HPA axis in response to acute stress, probably due to the prevention of excessive gut permeability (Ait-Belgnaoui et al., 2012). Recently, a two-strain probiotic, *L. helveticus* and *B. longum*, significantly improved measures of HPA axis responsiveness to CRD, an acute stressor, rather than with either strain alone (Ait-Belgnaoui et al., 2018). Conversely, infection with pathogenic *C. rodentium*, enhanced vulnerability to stress-induced memory impairments in mice, which was

ameliorated by pretreatment with a combination of probiotics (*L. rhamnosus* and *L. helveticus*) (Gareau et al., 2011).

Similar attenuation of stress responses has also been observed in chronic stress paradigms. For example, administration of *L. helveticus* NS8 to Sprague Dawley rats improved behavior following chronic restraint stress (Liang et al., 2015a). A different strain of *L. helveticus*, MCC1848, was also shown to ameliorate social defeat stress-induced anxiety- or depressive-like behaviors in mice (Maehata et al., 2019). L*. rhamnosus* abrogated anxiety-like behaviors due to chronic social defeat stress. However, the gut microbiota alterations that manifested due to the stressor remained unchanged (Bharwani et al., 2017). Another recent study has shown that supplementation with *L. plantarum* successfully abrogated heightened stress responses due to chronic unpredictable stress and sleep deprivation stress and resulting in increases in host gut Lactobacillus species (Dhaliwal et al., 2018). Likewise, administration of *C. butyricum* prevented depressive-like behaviors associated with chronic unpredictable stress (Sun et al., 2018).

The studies discussed so far were conducted in adult animals following acute or chronic stress, but probiotic treatments also ameliorate the effects of stress during vulnerable periods, such as in early-life stress. Several different probiotic strains have been tested in the maternal separation model with rats. A combination of *L. rhamnosus* and *L. helveticus* normalized fear behavior in stressed, maternally-separated pups and their later offspring (Callaghan et al., 2016; Cowan et al., 2016). The probiotic, *B. infantis,* normalized behavioral deficits in adult rats exposed to maternal separation (Desbonnet et al., 2010). Interestingly, the same strain did not affect depressive-like behavior in animals reared in a stress-free early environment (Desbonnet et al., 2008). Intervention with *B. animalis* and *Propionibacterium jensenii* restored some gut microbial perturbations in adult maternally-separated animals exposed to a "second hit" of stress in adulthood (Barouei et al., 2012). Finally, the administration of *B. bifidum* G9-1 concomitantly to the maternal separation stress prevented juvenile hypersensitivity to acute stress (Fukui et al., 2018).

The evidence for translating psychobiotic therapies into the clinic is becoming hard to ignore; studies are beginning to address the question of translation to humans. A combination probiotic *L. helveticus* R0052 and *B. longum* R0175 given to both rats and humans had an anxiolytic-like effect in rats and reduced urinary cortisol levels 24 hours following administration in humans, suggesting a normalization of the HPA axis response to stressors (Messaoudi et al., 2011a; Messaoudi et al., 2011b). Additionally, a study using the probiotic *L. plantarum* 299v resulted in decreased cortisol levels in a group of healthy adult students undergoing supplementation of probiotic during a period of exam stress (Andersson et al., 2016), and *L. plantarum* DR7 was shown to alleviate stress and anxiety in a randomized, double-blind, placebo-controlled study with stressed adults (Chong et al., 2019). A *B. longum* species, already proven to reduce anxiety and stress responses during acute stress in mice (Savignac et al., 2014), similarly reduced stress and anxiety measures in a population of healthy adults as well as improving cognition (Allen et al., 2016). Physical symptoms of exam stress, such as the onset of stress-induced GI symptoms and head-colds, proved amenable to probiotic treatment with *L. casei* (Kato-Kataoka et al., 2016) and *B. bifidum* (Langkamp-Henken et al., 2015). Studies in related IBS cohorts have also shown an improvement in stress-related GI symptoms due to probiotic treatments (Diop et

al., 2008). While not all potential probiotic interventions showing promise in preclinical studies have translated successfully to human studies (Kelly et al., 2017; Romijn and Rucklidge, 2015), there is enough evidence to warrant further investigation of potential probiotics as a therapeutic strategy to alleviate the detrimental effects of stress.

Prebiotics

Although it is accepted that certain prebiotics can alter the gut microbiota (Bindels et al., 2015; Dewulf et al., 2013), their effect on stress is less well understood. Administration of sialyl lactoses (human milk oligosaccharides) to mice exposed to social disruption prevented stress-induced colonic microbial disruption and anxiety-like behavior (Tarr et al., 2015). The prebiotics FOS and GOS have been shown to have anxiolytic effects in naïve animals, protecting mice from the impact of chronic stress on the microbiota (Burokas et al., 2017). In humans, one important small-scale placebo-controlled study in healthy individuals demonstrated that intervention with B-GOS® decreased waking salivary cortisol levels as well as increased positive processing of emotional information (Schmidt et al., 2015). In light of these results, it could be hypothesized that prebiotic intake could also modulate the HPA axis and have beneficial effects on stress-related disorders.

Other Microbiota Interventions

In addition to prebiotics and probiotics, other strategies to modify or deplete the microbiota have also been shown to alter stress responses. Although the mechanism is not clear, microbiota depletion using antibiotics has been shown to impact stress-related behaviors. Administration of non-absorbable antibiotics during pregnancy alters the maternal microbiota and can influence the behavior of the offspring, including increased anxiety-like behavior (Tochitani et al., 2016). However, prenatal and early postnatal administration of penicillin decreases anxiety-like behavior and sociability in a sex-specific way (Leclercq et al., 2017). Moving to a later time window of administration, exposure to antibiotics from early adolescence decreases anxiety and impairs cognition in mice (Desbonnet et al., 2015). However, antibiotics are not the only interventional strategy that can modulate stress related behavior. An FMT from stress-prone BALB/c to GF Swiss Webster mice increased anxiety-related behavior, whereas performing the transfer from the more stress-resilient Swiss Webster mice to GF BALB/c reduced the anxiety-like phenotype (Bercik et al., 2011a). Recently, FMT from mice exposed to chronic immobilization stress to conventional C57's induced anxiety-like behavior and suppressed hippocampal BDNF expression (Jang et al., 2018). From a more translational approach, FMT from depressed patients to microbiota-depleted rats was sufficient to increase anhedonia and anxiety-like behaviors in the rodent recipients (Kelly et al., 2016). Although these studies did not include any measurement of the neuroendocrine response to stress, they demonstrate that microbiota composition may play a causative role in stress-related behavioral changes. A clearer understanding is needed to elucidate the role neurohormones play in these behavioral outcomes. Intriguingly, excessive stress combined with the use of stomach acid suppressants have also been shown to additively and independently affect the composition of stomach microbiota (MacLaren et al., 2019). Indeed, multiple neurocognitive processes in the hippocampus were coincident with such changes in the microbiota composition (MacLaren et al., 2019).

XI. Diseases and Disease Processes

As the field of microbiota-gut-brain research has progressed and matured, the microbiota has been implicated in a growing list of psychological and neurological diseases and disease processes (**Fig. 7**). Of note, many disorders of brain and behavior are related to exogenous stressor exposure, dysregulation of the HPA axis stress response (see **Section IV. J.)**, and individual coping mechanisms, or resilience to stress, all of which are components of stress responding, that are now recognized as being modulated by the microbiota as described previously (see **Sections VI. G., VII. H.** and **X.D**). As we will outline below, the state of the evidence varies between disorders, with some in a preliminary stage of research where studies have been limited to correlational observations of altered microbiota composition in clinical populations, while there is stronger support for a causal role of the microbiota in other disease processes.

A. Autism Spectrum Disorder

Autism spectrum disorder is a heterogeneous group of neurodevelopmental disorders characterized by profound deficits in sociability, stereotyped or repetitive behavior in addition to anxiety and cognitive disturbances (Masi et al., 2017). With a worldwide prevalence of 1 in 68 children, it is more common in males, who are four times more likely to develop the condition than females (Mandic-Maravic et al., 2015). The behavioral disturbances are accompanied by profound alterations in key central physiological processes such as neuroinflammation, neurogenesis, neurotransmission and in the production of pro-social hormones, oxytocin and vasopressin (Sherwin et al., 2016b). Although ASD may be classically thought of as primarily neurological in its pathology, there is growing evidence to demonstrate a role for the GI system and its resident microbiota in aspects of ASD symptomatology also. Approximately 70% of children with ASD report comorbid GI disturbances such as bloating, constipation and diarrhea, indicating that gut physiology is indeed altered (Stephen et al., 2017). Interestingly, in a small open-label study in which children with ASD were treated with the broad-spectrum antibiotic, vancomycin, there was a marked improvement in behavioral symptoms (Kang et al., 2017; Sandler et al., 2000). Although antibiotics are not a viable long-term intervention strategy for the management of ASD, this study provided the field with a critical insight that the gut microbiota may contribute to the behavioral disturbances in this neurodevelopmental disorder. Several additional studies have observed significant alterations to the composition of the microbiota and in the production of microbial metabolites in children with ASD (Finegold, 2011; Finegold et al., 2010; Kang et al., 2018; Parracho et al., 2005; Wang et al., 2014). Of note, there is a reduced abundance of the beneficial bacteria genus, *Bifidobacterium*, along with an increased abundance of potentially pathogenic *Desulfovibrio* and *Clostridia* genera in the gut microbiota of children with ASD, a result that was consistent across all studies. A more recent study identified that the gene cpb2, which encodes for the clostridial toxin b, is significantly more expressed in *C. perfringens* isolated from the fecal microbiota of children with ASD relative to controls (Gora et al., 2018). The β2 toxin has been shown previously to cause GI-related illnesses (i.e., diarrhea) and the increased presence of this gene in clostridial species in the ASD microbiota may thus help to explain the GI-related comorbidities observed in this neurodevelopmental condition. While several studies to date have characterized the alterations of the microbiota in individuals with autism, there is limited evidence to demonstrate whether targeting the microbiota through probiotic or dietary interventions can improve symptoms of ASD in humans. However, a small

open-label clinical intervention demonstrated that FMT of a standardized microbiota cocktail to children with ASD was efficacious in improving the GI and behavioral symptoms (Kang et al., 2017). Although the sample size was small and the experimental design lacked a randomized, double-blind structure, the study provided promising preliminary evidence to demonstrate that the microbiota may indeed be a viable target as a treatment strategy for ASD. A more recent randomized, double-blind, placebo-controlled study demonstrated that a combination of a casein/gluten free diet along with the prebiotic, B-GOS®, led to an improvement in the behavioral symptoms of autistic children (Grimaldi et al., 2018). These behavioral changes were accompanied by an increase in the relative abundance of the beneficial strain, *B. longum*, in the microbiota of autistic children. Further clinical trials are required with larger sample sizes and more rigorous study design.

Preclinical studies have been invaluable in providing the field with an insight into how the microbiota-gut-brain axis may be involved in ASD. Knock out of the shank 3 (autism candidate) gene results in profound autistic-like behavior in mice (Sgritta et al., 2019; Tabouy et al., 2018) In addition to this, shank 3 transgenic mice also display alterations to the composition of their GI microbiota, with notable reductions in *Lactobacillus*, *Prevotella* and *Veillonella*. Interestingly, treatment with *L. reuteri* improved social deficits in male, but not female, shank 3 transgenic mice. This corresponded with an increased expression of oxytocin mRNA expression within the hypothalamus of male shank 3 transgenic mice. However, the probiotic strain reduced expression of the neuropeptide in the hypothalamus of female mice, which may explain the absence of any improvement in social behavior in these animals (Tabouy et al., 2018). Moreover, such results suggest that, other than modulation of oxytocin expression, there may sexual dimorphic factors underlying *L. reuteri*'s mechanism of action.

The BTBR mouse, which displays an inherent autistic-like phenotype across multiple behavioral domains also exhibits altered GI physiology similar to what is reported in the clinical setting (Golubeva et al., 2017). For instance, BTBR mice display prolonged intestinal motility indicative of constipation. Moreover, it has been reported that there is a breakdown in the permeability of the small and large intestine of these animals (Coretti et al., 2017). This permeability deficit phenomenon may contribute towards bacterial or related component, translocated to systemic circulation, whereby they can elicit an inflammatory response (Golubeva et al., 2017). Profound alterations in the microbiota composition characterized by deficits in the relative abundance of *Bifidobacterium* and *Blautia* genera are also observed compared to C57BL/6 mice. The absence of these two bacterial genera was linked to additional deficits in bile acid signaling in these mice, which may contribute towards its observed GI physiology.

While genetic models such as the Shank 3 and BTBR are important tools in elucidating any genetic component to the alterations in the microbiota-gut-brain axis in ASD, it is also vital to model how environmental factors may contribute towards the neurodevelopmental disorder and their impact upon the GI microbiota. For instance, *in utero* exposure to the viral component and TLR3 agonist, Poly I:C, facilitated the development of autistic-like behavior in mice, while also increasing intestinal permeability and altering the composition of the gut microbiota (Hsiao et al., 2013). Moreover, exposure to the teratogen valproic acid (VPA) *In utero* has been shown to result in intestinal inflammation (Rosenfeld, 2015), and dysregulation to the GI microbiota observed as changes in the Firmicutes: Bacteroidetes ratio (de Theije et al., 2014c) and an increase in the

abundance of the species *Desulfovibrio* (Finegold, 2011)DNA</keyword></keywords><dates><year>2011</year><pub-dates><date>Aug</date></pub-dates></dates><isbn>1532-2777 (Electronic. Further, VPA exposure leads to a deficit in social interaction in mice while also affecting serotonergic turnover in the amygdala (de Theije et al., 2014b; de Theije et al., 2014c). Given the influence that the microbiota has upon central processes such as serotonergic neurotransmission (O'Mahony et al., 2015), alterations to the gut microbiota through environmental insults such as in utero VPA or Poly I:C exposure may contribute towards the observed behavioral deficits in these models. Further, considering the neuroactive properties of microbial metabolites, such as SCFAs (Stilling et al., 2016), their role in modulating autism-related behavior should not be overlooked. Indeed, several preclinical studies have documented how neurotoxic doses of the SCFA propionic acid induces autism-like behavior in rodents (MacFabe et al., 2011; Shultz et al., 2015). Whether elevated levels of SCFAs, such as propionate, contribute towards what is observed clinically in autistic individuals is unknown but warrants further attention. Further, while studying the loss-of-function mutation in the histone demethylase KDM5 *Drosophila* found in ASD, social behavior appears to be modulated via immunoregulation and microbiota maintenance (Chen et al., 2019).

Preclinical models of ASD have also provided considerable information into the potential efficacy of candidate probiotic strains in improving autism-related behavior and their underlying mechanism of action (Sgritta et al., 2019). Mice from mothers fed a HFD during pregnancy exhibit deficits in social behavior and social cognition (Buffington et al., 2016). Analysis of the microbiota of these mice revealed the absence of several key lactobacillus species. Interestingly, supplementation of one of these strains, *L. reuteri*, in mice from mothers fed a HFD resulted in a restoration of their behavioral deficits that was also associated with an increase in expression of the prosocial hormone, oxytocin, in the PVN of the hypothalamus (Buffington et al., 2016). The finding that *L. reuteri* increases oxytocin production has been shown to be dependent upon the integrity of the vagus nerve in addition to IL-10 signaling (Poutahidis et al., 2013; Varian et al., 2017).

Other candidate probiotic strains have been shown to improve other facets of autism-related behavior in animals. For instance, in the maternal immune activation model of ASD *B. fragilis* administration early in life resulted in an improvement in stereotyped and anxiety-like behavior, but not in sociability (Hsiao et al., 2013). Given that each bacterial species possesses its own unique biochemical properties, these contrasting effects of potential probiotics on autism-related behaviors are most likely due to such strains modulating different aspects of the microbiota-gut-brain axis (e.g. immune system, vagus nerve, microbial metabolites, peptides, etc.).

Y. Major Depressive Disorder (MDD)

Depression is the leading cause of disability worldwide, affecting 4.4% of the world's population (World Health Organization Human Reproduction Programme, 2015). It is now known that Major Depressive Disorder (MDD) correlates with increases in pro-inflammatory cytokines (Ticinesi et al., 2017), which in turn activate the HPA axis possibly accentuating its hyper-activation associated with depression (Chopra et al., 2011). Effective therapies for depression abrogate the heightened inflammatory response and decrease HPA

axis activation (Chopra et al., 2011; Pariante, 2017).

There is burgeoning evidence of a role for the microbiota-gut-brain axis in MDD (Foster and McVey Neufeld, 2013; Horne and Foster, 2018). However, there is a need for better-designed studies with clear psychiatric and psychological phenotyping when it comes to depression and anxiety and the microbiota-gut-brain axis in patient populations. Currently, most of the studies have been conducted in preclinical models (Dinan and Cryan, 2017). As stated earlier alterations in the microbiota composition and inflammation has been seen in the maternal separation model (O'Mahony et al., 2009) and the Flinders sensitive rat model of depression (Tillmann et al., 2018). Evidence from GF mice has provided further insight into the role of the microbiota-gut-brain axis in depression, showing that the absence of a microbiota reduces depressive-like behavior in the forced swim test (FST) (Zheng et al., 2016a). Certain probiotic and prebiotic interventions have also been shown to reduce depressive-like behaviors in rat and mouse models, in addition to ameliorating inflammatory responses (Bravo et al., 2011; Burokas et al., 2017; Desbonnet et al., 2010; Tillmann et al., 2018) (see **Table's 4 and 5**).

There are now a number of human studies that have found differences in fecal microbiota in MDD patients when compared to healthy controls (Aizawa et al., 2016; Jiang et al., 2015; Kelly et al., 2016; Naseribafrouei et al., 2014; Zheng et al., 2016a). However, there is limited consensus between them in relation to the type of changes seen. In one study, Bifidobacterium and Lactobacillus were reduced in 43 depressed individuals (Aizawa et al., 2016). Another study witnessed increased fecal bacterial α-diversity, present in a cohort of 46 concurrently depressed patients, which was not seen in patients who had responded to treatment (Jiang et al., 2015). One observation noted that Bacteroidetes, Proteobacteria, and Actinobacteria were increased, and Firmicutes were decreased, and negatively correlated with severity of the depressive symptoms (Jiang et al., 2015). While inter-individual variability was apparent, there were significant differences found in a variety of genera when compared to controls. The order Bacteroidales were significantly increased, and the family Lachnospiraceae were significantly decreased in another cohort of 37 depressed patients versus healthy controls (Naseribafrouei et al., 2014)Hedmark University College, Hamar, Norway.</auth-address><titles><title>Correlation between the human fecal microbiota and depression</title><secondary-title>Neurogastroenterol Motil</secondary-title></titles><pages>1155-62</pages><volume>26</volume><number>8</number><edition>2014/06/04</edition><keywords><keyword>Adult</keyword><keyword>Depressive Disorder/*microbiology</keyword><keyword>Feces/*microbiology</keyword><keyword>Female</keyword><keyword>Humans</keyword><keyword>Male</keyword><keyword>*Microbiota</keyword><keyword>Middle Aged</keyword><keyword>RNA, Ribosomal, 16S/genetics</keyword><keyword>16SrRNA gene</keyword><keyword>Illumina deep sequencing</keyword><keyword>depression</keyword><keyword>gut microbiota</keyword></keywords><dates><year>2014</year><pub-dates><date>Aug</date></pub-dates></dates><isbn>1365-2982 (Electronic, at the moment, all correlative. Elevated cortisol output in addition to decreased fecal microbial richness was reported in a study of 34 MDD patients (Kelly et al., 2016), and significantly different gut microbiota were noted in an MDD cohort when compared to matched controls (Zheng et al., 2016a). Furthermore, a human FMT to rats resulted in a transfer of the depressive and anxious phenotypes (Kelly et al., 2016; Zheng et al., 2016a), which was not observed with FMT from healthy human controls. Currently, it is difficult to reconcile the variations seen across the studies and it may be reflective

of the small sample size as well as medication effects. Largescale studies in drug naïve depressives is now warranted.

In an effort to address this a recent study examined the microbiota composition of > 1,000 individuals enrolled in Belgium's Flemish Gut Flora Project and clustered individuals into four enterotypes based on their microbiome composition (1534). Intriguingly, those who had depression, or lower quality of life score were over represented in an enterotype characterized by lower relative abundance of the genus Faecalibacterium, in addition to an overall reduced microbial load. On deeper analysis, the researchers found that there was an association between bacteria that produce the SCFA butyrate (*Faecalibacterium* and *Coprococcus*) and higher quality of life indicators. On the other hand, the levels of *Coprococcus* and *Dialister* were significantly lower in people with depression. Many of the findings were replicated the Dutch LifeLinesDEEP cohort as well as in a small cohort of clinically refractory depressed patients. Additionally, identified potential microbial-derived metabolites that have neuroactive potential from the literature, identified relevant pathways in the shotgun metagenome data, and clustered them into a modular framework. In total, they curated and annotated 56 different gut–brain modules, each corresponding to a single neuroactive compound production or degradation process. These included modules involved in the potential ability of the gut microbiome to synthesize the dopamine metabolite 3,4-dihydroxyphenylacetic acid (DOPAC). Two other modules relevant to glutamate and GABA pathways also tended to be altered in depression. Interestingly, bacteria that have the capacity to generate or breakdown GABA have been implicated in changes in brain function and behaviour (108, 1206, 1429). Although still correlative, they are among the most convincing to date to show a relationship between microbiota composition and mental health. Moreover, they agree with recent crowdsourced funding approaches such as the American Gut Project, which have shown a link between microbiota composition with depression (1015).

A probiotic intervention study using an *L. casei* strain described improvements to mood ratings in a healthy elderly cohort following treatment, with most benefit for those who had lower mood at baseline (Benton et al., 2007). Furthermore, a triple-strain probiotic (*L. acidophilus*, *L. casei*, and *B. bifidum*) resulted in improvements in depression scores, in addition to beneficial metabolic effects in an MDD cohort (Akkasheh et al., 2016). Importantly, *L. rhamnosus* HN001 supplementation during pregnancy resulted in significant lowering of anxiety and postnatal depression (Slykerman et al., 2017). One recent study examined the effects of the prebiotic GOS combined with a probiotic containing *L. helveticus* and *B. longum* on mild to moderate MDD in a placebo-controlled parallel study (Kazemi et al., 2019). Beneficial effects of the probiotic were observed, including decreases in depression scores as well as improvements in tryptophan signaling. Another recent open-label study in patients with treatment-resistant depression has shown promise for the probiotic *C. butyricum* as an adjunct therapy, used in combination with anti-depressant drugs (Miyaoka et al., 2018). Cognitive performance was further enhanced upon treatment of MDD patients with the probiotic *L. Plantarum* 299v (Rudzki et al., 2019).

Several studies in the literature failed to show any benefit to depression scores upon administration of probiotics in patients presenting with MDD (Chung et al., 2014; Romijn et al., 2017). However, promising results

in healthy controls and preclinical studies warrant further investigation in clinical populations (Messaoudi et al., 2011a; Messaoudi et al., 2011b). Overall, systematic reviews of probiotics as a potential adjunct therapy in MDD are encouraging, describing that probiotics effectively improve mood in humans (Huang et al., 2016; Pirbaglou et al., 2016; Wallace and Milev, 2017) although another recent meta-analysis calls into question the significance of these findings, highlighting the confounding comparability of studies due to strain differences and severity of disease (Ng et al., 2018). It is of note that poor diet is now accepted as a risk factor for depression, as well as a therapeutic target (Jacka, 2017; Jacka et al., 2017). Improvements in diet will likely lead to an increase in consumption of prebiotic foods. There are limited studies on the effects of prebiotics in depression. Nonetheless, there is some evidence for a reduction of stress in human studies, which is intrinsically linked with depression (Schmidt et al., 2015; Silk et al., 2009). One study recently described no benefit from an eight-week GOS interventional therapy for mild to moderate MDD (Kazemi et al., 2019). Polyphenols, such as resveratrol, have been described to reduce depressive-like behaviors, in addition to ameliorating increases in corticosterone and pro-inflammatory cytokines (Yang et al., 2017), preclinically. Curcumin has described benefits in MDD patients (Ng et al., 2018), but further clinical studies on potential benefits of polyphenols in MDD are needed.

Z. Anxiety

Anxiety and depression frequently go hand-in-hand, and most studies of the microbiota-gut-brain axis in anxiety include measures of depression and vice versa. Much of the evidence for a link between anxiety and the microbiota-gut-brain axis comes from preclinical studies (Foster and McVey Neufeld, 2013), whereby an anxious-like phenotype may be inferred from the animal's behavior in certain environments, such as the open-field test, elevated plus maze, light/dark box, or in reaction to certain stressors (see **Tables 2-5**). GF mice display diminished anxiety-like behavior in comparison with conventionally reared animals (Clarke et al., 2013; Diaz Heijtz et al., 2011; Neufeld et al., 2011) alongside exaggerated corticosterone responses to stress indicating altered HPA-axis function, although GF rats exhibit exaggerated anxiety responses (Crumeyrolle-Arias et al., 2014). It is important to note that changes in anxiety due to probiotic treatment are species and strain-dependent (Bravo et al., 2011; Savignac et al., 2014).

Improvements in specific anxiety measures have been shown in a small number of probiotic intervention studies of healthy control participants (Messaoudi et al., 2011b) and in chronic fatigue syndrome (Rao et al., 2009). Furthermore, a multi-strain probiotic (*S. thermophilus (2 different strains)*, *L. bulgaricus*, *L. lactis* subsp. *Lactis*, *L. acidophilus*, *L. plantarum*, *B. lactis*, *L. reuteri*) was recently demonstrated to have anxiolytic effects in a small study of healthy controls (Colica et al., 2017). Interestingly, B-GOS® significantly improved anxiety levels in individuals with IBS (Silk et al., 2009). Intriguing recent work has identified *Lactobacillus plantarum DR7* as a possible psychobiotic, where it alleviated anxiety and stress associated symptoms in a randomized, double-blind, placebo-controlled study (Chong et al., 2019). However, there is a clear need for further translational studies to specifically examine the effects of psychobiotics on anxiety.

AA. Schizophrenia

Schizophrenia is a complex and heterogeneous debilitating neural disorder, which has proven to be one of the most difficult psychiatric conditions to treat. It is characterized by both positive and negative neurobehavioral dysfunctions including, but not limited to, psychosis, cognitive dysfunction, delusion, apathy, and social withdrawal (Owen et al., 2016). There have been ideas circulated purporting a role for the GI tract immune response in the pathogenesis of schizophrenia (Patterson, 2009; Severance et al., 2015; van Kesteren et al., 2017), where risk factors include *Toxoplasma gondii* infection, food intolerances, GI inflammation and cell barrier defects. There is evidence for both genetic and environmental etiological factors in the presentation of schizophrenia symptoms (Demjaha et al., 2012; European Network of National Networks studying Gene-Environment Interactions in et al., 2014). As a result of the immune system role associated with this psychotic disease and the key role the microbiota plays in establishing and maintaining immune function, much recent effort has examined possible influences of the microbiota in schizophrenia (Belkaid and Hand, 2014; Hooper et al., 2012; Schwarz et al., 2018). One recent study performed a metagenomic analysis of the oropharyngeal microbiota in schizophrenic individuals and healthy controls, identifying large differences at the phylum and genus levels (Castro-Nallar et al., 2015). Proteobacteria, Firmicutes, Bacteroidetes, and Actinobacteria presented with the most divergence between the two cohorts, with the fungi Ascomycota present in greater abundance in schizophrenia patients. Further, α-diversity was decreased in medicated and unmedicated patients, and FMT into germ-free mice had reduced hippocampal glutamate, and increased levels of glutamine and GABA, suggesting that the schizophrenic microbiome itself can affect neurochemistry, which may be relevant to the human condition (Zheng et al., 2019). Intriguingly, antibiotic use reduced microglia-mediated synapse engulfment in an *in vitro* assay, where reduced synapse density is a hallmark seen in postmortem cortical tissue from schizophrenia patients (Sellgren et al., 2019). Upon examining electronic health records of a cohort of young adults, minocycline usage correlated with a modest decrease in incident schizophrenia (Sellgren et al., 2019), indicating that much more work is needed to examine the involvement of the microbiome in schizophrenia.

No study has yet proven successful in altering any positive or negative behavioral symptoms while examining the potential for probiotic intervention in schizophrenia, in line with the severe nature and complexity of the disorder. However, some reports have indicated that at least some probiotic-induced alleviation of bowel problems commonly associated with schizophrenia are possible. In one human study, severe bowel difficulty was reduced over the course of the trial in a small group of outpatients (Dickerson et al., 2014), even though there were no assessed psychiatric symptoms altered. Further, another human study found an association between levels of *Candida albicans* and gut discomfort (Severance et al., 2017), where a trend for improved positive psychiatric symptoms occurred in males treated with a probiotic formulation (containing *L. rhamnosus* GG and *B. animalis* subsp. *lactis* Bb12), and who were seronegative for *Candida albicans.* Combined, accruing information is helping uncover a whole new array of potential treatment options for severe psychiatric illness, including consideration of bowel comfort in therapeutic analyses. More work is needed to increase the understanding of microbiota-gut-brain axis contributions in schizophrenia, increasing sample size and longitudinal analysis.

AB. Bipolar Disorder

Another serious neuropsychiatric illness, bipolar disorder is also hypothesized to have some origin associated with microbiota influence (Bengesser et al., 2019). Implications for the microbiome have emerged whereby patients presenting with bipolar mania were nearly twice as likely as other patients to have been recently treated with systemic antibiotics (Yolken et al., 2016). Fecal microbiome analysis has identified decreased abundance of Firmicutes, specifically *Faecalibacterium,* in patients presenting with bipolar disorder (Evans et al., 2017), which also correlated with self-reporting symptom severity, indicating a potential therapeutic avenue for these people. In a first of its kind, a recent probiotic clinical intervention indicated that probiotic therapy could reduce the rate of rehospitalization of patients who were recently discharged following hospitalization for mania (Dickerson et al., 2018).

AC. Anorexia Nervosa & Cachexia

Anorexia nervosa has one of the highest mortality rates amongst psychiatric illnesses with the greatest impact on quality of life (Arcelus et al., 2011; Huas et al., 2011). It is characterized by a perverted self body-image resulting in self-imposed food intake restriction leading to subsequent severe weight loss, associated with hyperactivity and hypothermia (Hebebrand et al., 2003). Currently, there is no definitive understanding of its etiology, nor are there any effective medication. Further, there is no clear gut microbiota role or involvement ascribable in this disorder. Nonetheless, some recent evidence has seen potential gut microbiota involvement and identifies it as a possible intervention target (for reviews see (Kleiman et al., 2015; Ruusunen et al., 2019).

Cachexia is a metabolic condition characterized by the loss of skeletal muscle mass, both dependent and independent of fat mass loss and is usually associated with severe illness including cancer and AIDS (Fearon et al., 2013). The pathophysiology of cancer cachexia includes reduced food intake and abnormal metabolism, leading to a negative energy/protein balance (Fearon et al., 2011), where the primary drivers are mediated via inflammatory pathways and the CNS (Fearon et al., 2013). However, the role of the microbiota in shaping such responses needs further attention.

AD. Addiction

Recent research has investigated the microbiota-gut-brain axis in the context of addiction, which is defined as a chronic relapsing disorder where an individual continues to engage in a maladaptive behavior, despite negative consequences (Koob, 2015). Most studies to date have focused on the impact of drug use on the gut microbiota. In addition to drugs of abuse having a direct effect on gut microbiota (Peterson et al., 2017), addiction includes a myriad of comorbidities that have previously been linked to the microbiota-gut-brain axis, including stress and anxiety (Bailey et al., 2011; Bravo et al., 2011; Burokas et al., 2017; Xiao et al., 2018), depression (de Timary et al., 2015; Temko et al., 2017), and chronic inflammation (Allais et al., 2016; Lee et al., 2018b; Littman and Pamer, 2011; Lowe et al., 2017; Panduro et al., 2017).

The impact of substance abuse on the microbiota has been most extensively studied in alcohol abuse. Research has linked alterations in gut microbiota during alcohol consumption to increased intestinal permeability and hepatic inflammation (Bjorkhaug et al., 2019; Chandler J.A. et al., 2018; Lowe et al., 2017),(Bull-Otterson et al., 2013; Llopis et al., 2016; Mutlu et al., 2009; Mutlu et al., 2012; Yan et al., 2011), but a reduced gut microbiome can also protect from alcohol-induced neuroinflammation resulting in the alteration of intestinal and brain inflammasome expression (Lowe et al., 2018b). Preclinical supplementation with *L. rhamnosus* GG has been shown to lessen the severity of alcoholic hepatitis (Bull-Otterson et al., 2013). Furthermore, altered microbiota composition with alcohol administration occurs not only with oral, but also vapor administration (Peterson et al., 2017), indicating that other non-orally administered drugs of abuse have the potential to impact the microbiota. Phenotyping of compulsive alcohol-seeking behavior shows intriguing correlations between specific gut bacteria and striatal dopamine expression in rats (Jadhav et al., 2018). Clinical research has linked negative affect during alcohol withdrawal to increased intestinal permeability, inflammation, and microbiota composition (Leclercq et al., 2014).

Available data on the effects of other substances of abuse on the gut microbiota indicate similar effects to alcohol. Clinical studies investigating tobacco smokers have associated smoking and cessation to changes in the gut microbiome and inflammation (Allais et al., 2016; Benjamin et al., 2012; Biedermann et al., 2014; Biedermann et al., 2013). Chronic exposure to tobacco smoke in mice alters the microbiome and mucin gene expression (Allais et al., 2016). Murine-models of opioid use have suggested a role for gut microbiota in the progression of morphine-dependence and disruption of GI function (Kang et al., 2017; Lee et al., 2018b; Plein and Rittner, 2018; Wang et al., 2018a). Also, studies have linked the microbiota to altered intestinal permeability, inflammation, and metabolic processes in opioid-treated mice (Kang et al., 2018; Lee et al., 2018b; Wang et al., 2018a). In a place preference task rodents that received methamphetamine where shown to have reduced abundance in a genus of propionate-producing bacteria as well as decreases in propionate, compared to saline controls (Ning et al., 2017)China.</auth-address><titles><title>Gut Microbiota Analysis in Rats with Methamphetamine-Induced Conditioned Place Preference</title><secondary-title>Front Microbiol</secondary-title></titles><periodical><full-title>Front Microbiol</full-title></periodical><pages>1620</pages><volume>8</volume><edition>2017/09/12</edition><keywords><keyword>16S rRNA gene sequencing</keyword><keyword>gut microbiota</keyword><keyword>methamphetamine</keyword><keyword>propionates</keyword><keyword>short chain fatty acids</keyword></keywords><dates><year>2017</year></dates><isbn>1664-302X (Print. Prolonged administration of a non-absorbable antibiotic in rodents enhanced cocaine place preference and locomotor sensitivity at low doses (5mg/kg) of cocaine, but this effect was not seen at higher doses (10mg/kg) (Kiraly et al., 2016). Interestingly, antibiotic intervention in alcohol and opioid studies reduced drug-associated increases in intestinal permeability, inflammation, and enteric neuron signaling (Kang et al., 2017; Lowe et al., 2017). Chronic treatment with the major psychoactive constituent of cannabis, Δ9-tetrahydrocannabinol (THC), changed gut microbiota composition in mice (Cluny et al., 2015). These changes contributed to a reduction in energy intake and prevention of HFD-induced increases in body weight and adiposity. This preliminary research suggests that there is an intriguing connection between gut microbiota and addiction. However, much work is still needed to definitively illustrate that gut microbiota composition can influence addictive behavior. Future research will need to investigate microbiota composition prior to drug administration in order to eliminate the confound of drug-induced microbiota changes and define “at risk” addictive phenotypes. The identified “at risk” pheno-

types should be studied longitudinally to investigate how the microbiota changes before drug administration, during, and following abstinence. Furthermore, this mechanism should be investigated with a focus on the dopaminergic system, which is intricately involved in reward learning, locomotor sensitivity, and reinforcement of addictive behavior (Rudzki et al., 2019)

AE. Attention Deficit Hyperactivity Disorder (ADHD)

Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder that presents as inattention (i.e., difficulties in organization and focus), hyperactivity and impulsivity, or a combination of both (American Psychiatric Association, 2013). As yet there are limited studies on the role of the microbiome in ADHD but there is a long history of investigations into the effects of diet on ADHD symptoms, with a Western-style diet being considered a predisposing factor for the disorder (Howard et al., 2011) and elimination diets, particularly exclusion of artificial food color, resulting in positive outcomes (Millichap and Yee, 2012; Pelsser et al., 2017; Pelsser et al., 2011). As discussed in Section VIII.IX, diet has a profound influence on the gut microbiota (Gutierrez-Martos et al., 2018; Ma et al., 2014; Rincel et al., 2018), suggesting that the microbiota may play a role in ADHD symptomology (Sandgren and Brummer, 2018). An analysis of a small clinical cohort of adults and adolescents presenting with ADHD supported this hypothesis, finding an increase in the genus *Bifidobacterium* compared to healthy controls, potentially via differential regulation of gut-based dopamine precursors (Aarts et al., 2017). Promisingly, a perinatal probiotic intervention reduced risk for ADHD diagnosis later in childhood (Partty et al., 2015), reflecting the potential for microbiota-based interventions in ADHD.

AF. Post-Traumatic Stress Disorder (PTSD)

Despite strong preclinical and recent clinical evidence, for microbiota modulation of acute and chronic stress (see **Section's VI. G.** and **VII. H.**), direct investigations of the microbiota in clinical PTSD have been lacking; nonetheless, conceptually PTSD has been receiving increasing attention to be a target for microbiome-based strategies (Leclercq et al., 2016). Several authors have hypothesized that there is a link between PTSD and the microbiota, yet to our knowledge, there has been only one published study (Hemmings et al., 2017). Further investigation into the human gut microbiome profile in situations of chronic stress is warranted.

AG. Obsessive-Compulsive Disorders (OCD)

Much speculation currently surrounds the possible involvement of the gut microbiota in obsessive-compulsive disorders (OCD; (Rees, 2014; Turna et al., 2016); however, little current research exists. Stress and exposure to antibiotics both of which affect microbiota composition are proposed mechanisms coinciding with the onset of symptoms in patients presenting with OCD (Karakas Ugurlu et al., 2013), both of which have been shown to negatively impact gut microbiota (Foster et al., 2017; Guida et al., 2018). Further, rodent behavior in the marble-burying test, which highlights perseverative, compulsive and repetitive actions, can be influenced by the implementation of pre- and pro-biotics suggesting a potential therapeutic benefit in future OCD treatment (Kantak et al., 2014; Nishino et al., 2013; Savignac et al., 2014). Clearly more longitudinal human studies are needed to understand to what extent the microbiome is contributing to the symptoms of

OCD (Rees, 2014; Turna et al., 2016).

AH. Obesity

Obesity is a major public health issue, increasing risk for a range of serious health problems and ultimately increasing morbidity of the individual at a substantial economic cost to society (Tremmel et al., 2017). Obesity is known to express comorbidly with other centrally regulated disorders such as depression (Carey et al., 2014), bipolar disorder (Goldstein et al., 2013b), anxiety disorders (van Dammen et al., 2018) and altered social behavior (Leroux et al., 2013). Alarmingly, the prevalence of obesity has increased recently in many countries worldwide, particularly countries where a Western-style diet is dominant ((NCD-RisC), 2016). As described earlier (see **Section's VIII. C** and **X. A**.), the microbiota is highly influenced by diet (Marungruang et al., 2018)and plays a key role in the central regulation of food intake. Thus, it is not surprising that the microbiota is also implicated as a key factor in obesity (For review see (Bruce-Keller et al., 2015; Castaner et al., 2018; Cox et al., 2015; Torres-Fuentes et al., 2017)). To date, most of the focus on microbiota-obesity interactions have focused on adiposity, glycemic response, and peripheral regulation of metabolism. However, there is a growing appreciation that the microbiota-gut-brain axis is involved (Sugino et al., 2019; Torres-Fuentes et al., 2017). For example, over the course of a single day, the gut microbiota of humanized mice can experience a shift in both composition and function which may explain the influence of the westernized diet in obesity (Turnbaugh et al., 2009)Inbred C57BL</keyword><keyword>Molecular Sequence Data</keyword><keyword>RNA, Ribosomal, 16S/genetics</keyword></keywords><dates><year>2009</year><pub-dates><date>Nov 11</date></pub-dates></dates><isbn>1946-6242 (Electronic. Through both human and mouse models of obesity, an alteration in microbiota composition is observed, namely an increase in the relative abundance of Firmicutes and a decrease in Bacteroidetes compared to lean controls. Interestingly this observation is reversed when individuals are put on a lower calorie diet, which has been shown to affect metabolic potential and increase the capacity to harvest energy from food (Turnbaugh et al., 2006; Turnbaugh et al., 2009).

The presence of food in the gut results in a cascade of signaling events that is essential in regulating energy homeostasis. Vagal afferent neurons facilitate communication between the gut and the brain via NTS (Berthoud, 2008b). In obese rat models, a reduction in c-fos activation in the NTS is seen following food intake, suggesting a decrease in vagal signaling from the gut to the NTS (Covasa et al., 2000). Sensitivity of the vagal nerve to peripheral neuropeptides involved in food intake is also seen in diet-induced obesity (Daly et al., 2011) with vagal neurons becoming resistant to leptin, reducing its sensitivity to CCK and subsequently affecting the regulation of meal size (de Lartigue et al., 2012). Given the role of the vagus in signaling from microbiota to brain it is highly likely to also play a role in microbial regulation of food intake.

Bariatric surgery is an alternative intervention often used to treat morbid obesity and has been shown to alter the gut microbiota (Aron-Wisnewsky and Clement, 2014; Kong et al., 2013). This surgery has been shown to increase the hormonal and inflammatory status, reduce adiposity and improve insulin sensitivity, as well as increase the bile acid pool and microbiota composition diversity (Aron-Wisnewsky and Clement,

2014). The overall abundance of Gammaproteobacteria and Verrucomicrobia (*Akkermansia*) was increased, and Firmicutes decreased, in both human (Aron-Wisnewsky and Clement, 2014) and rodent (Zhang et al., 2009) bariatric studies. In one intriguing study, FMT from mice that underwent gastric bypass surgery into GF animals resulted in decreased fat mass and an overall reduction in body weight in the GF mice (Liou et al., 2013). From this study one can hypothesize that bariatric surgery can lead to alterations in gut microbiota, resulting in variations in SCFA composition, which in turn can affect host metabolism, gut hormone secretion, and insulin sensitivity. Thus, targeting these effects could play a central role in treating obesity, metabolic syndrome, and diabetes. For review see (Aron-Wisnewsky and Clement, 2014; Berthoud, 2008b). Compounding the potential success of bariatric surgery for treating obesity, post-operative treatment with a course of probiotics has been shown to increase bacterial diversity and enhance further weight loss (Woodard et al., 2009).

Orexigenic peptides such as ghrelin are known to be altered in obesity, notably circulating ghrelin is decreased in obese patients indicating changes to ghrelin synthesis in the gut and possible upregulation of the ghrelin receptor (Tschop et al., 2001). Oxyntomodulin, an anorexigenic gut-derived hormone is being considered a viable target for obesity treatment (Wynne et al., 2006). For example, oxyntomodulin has been shown to reduce food intake resulting in weight loss, and reduced sensitivity and expression of anti-obesity gut-derived peptides, and is observed within the hypothalamus when conventionally raised mice are compared to leaner GF mice (Schele et al., 2013). Given the role of gut peptides in signaling from microbiome to brain (see **Section IV**) they are poised to play a key role in microbial regulation of food intake too, but more research is needed to delineate the exact nature of this crosstalk

A common side-effect of many medications includes a change in patient bodyweight and as described earlier in **Section IX. F.** many of these medications also affect microbiota composition. For example, atypical antipsychotics are known for weight gain and metabolic dysfunction as prominent side-effects (Birkenaes et al., 2008; Citrome et al., 2011; Davey et al., 2013; Davey et al., 2012; Morgan et al., 2014; Oriot et al., 2008; Perez-Iglesias et al., 2009). Moreover, a recent prebiotic approach was also shown to reverse olanzapine-induced weight gain (Kao et al., 2018). Risperidone, a second-generation antipsychotic often prescribed for the treatment of schizophrenia and bipolar disorder in children and adolescents (Bishop and Pavuluri, 2008), has been shown to upregulate pathways involved in weight gain, and alter gut microbial composition after chronic treatment (Bahra et al., 2015). Furthermore, this phenotype was transmissible via FMT as well as through treatment with phages that was isolated from risperidone-treated microbiota (Bahra et al., 2015). Future focus will concentrate on developing probiotic and prebiotic interventions which act on the gut microbiota composition to restore normal gut-brain signaling to act as novel treatments for obesity (Torres-Fuentes et al., 2017).

AI. Irritable Bowel Syndrome (IBS)

IBS is one of the most common types of functional gastrointestinal disorder (FGID) and can significantly impact quality of life for these patients. Symptoms include alterations in bowel habits, abdominal pain, bloat-

ing, distention and excessive flatulence (Enck et al., 2016; Saha, 2014). In addition, IBS frequently presents co-morbidly with behavioral, psychosocial, psychological and environmental factors (Jeffery et al., 2012a; Rodino-Janeiro et al., 2018; Stanisic and Quigley, 2014) with microbiota-gut-brain interactions being a prime target in patients with IBS (Collins, 2014; Kennedy et al., 2014; Mayer et al., 2015a). Moreover, with the advent of Rome IV criteria, IBS has been formally recognized as a disorder of the gut-brain axis (Collins, 2014; Quigley, 2018), with a possible role for diet-microbiota interactions in the genesis of core symptoms (Rajilic-Stojanovic et al., 2015).

One particular pathway of importance in IBS is that of 5-HT signaling. As described earlier (**Section VII.D**), it has been demonstrated that a functional GI-tract involves 5-HT signaling between ECs (Mawe et al., 2006; Mawe and Hoffman, 2013) acting as sensory transducers and the majority of 5-HT is synthesized, stored, and released by these cells, which interact with intrinsic and extrinsic sensory nerve afferents in the mucosal layer of the gut (Demjaha et al., 2012; Severance et al., 2015). Any change to this signaling can result in altered gut function, especially when considering EC-directed gut 5-HT signaling controls many GI functions including secretion, vasodilation, peristalsis as well as sensory perception such as pain and nausea (Belkaid and Hand, 2014; Castro-Nallar et al., 2015; European Network of National Networks studying Gene-Environment Interactions in et al., 2014; Hooper et al., 2012; Schwarz et al., 2018). Moreover, serotonergic function and tryptophan metabolism is known to be altered in IBS patients (Anderson and Maes, 2015; Clarke et al., 2009; Clarke et al., 2012b; Dacquino et al., 2015; Dickerson et al., 2014; Fitzgerald et al., 2008; Lichtenstein et al., 2009; Severance et al., 2017).

Microbial- and diet-based treatments for IBS have given cause for hope (Dimidi et al., 2017; Simren and Tack, 2018; Whelan et al., 2018). A probiotic-based clinical treatment has been shown to be effective in ameliorating stress-related GI complaints when using a combination of *L. acidophilus* Rosell-52 and *B. longum* Rosell-175 (Diop et al., 2008). Another study reported marginally increased positive outlook scores in patients with IBS *B. longum*, indicative of reduced depression (Pinto-Sanchez et al., 2017b). However, a study using a *L. rhamnosus* strain failed to find benefits on depression scores in another cohort of IBS patients (Dapoigny et al., 2012). It has been proposed that probiotic amelioration of IBS symptomology may be acting indirectly through an anti-inflammatory mechanism (Ticinesi et al., 2017; World Health Organization Human Reproduction Programme, 2015). Such anti-inflammatory mechanisms may also be partially responsible for the positive effects of dietary restriction, such as that seen in the low FODMAP (fermentable oligosaccharides, disaccharides, monosaccharides and polyols) diet in IBS (Chopra et al., 2011; Dinan and Cryan, 2017; Foster and McVey Neufeld, 2013). Here, it is believed that high doses of certain FODMAPs can result in increased luminal water in the small intestine (Marciani et al., 2010; Murray et al., 2014), or increased colonic gas production resulting from microbiota fermentation (Murray et al., 2014; Ong et al., 2010), which can lead to pain, bloating and diarrhoea. An alternate method for IBS treatment involves FMT from non-IBS individuals to patients with IBS (Halkjaer et al., 2018; Holvoet et al., 2017). FMT has become a popular treatment method for IBS (Mizuno et al., 2017; Pinn et al., 2015; Zheng et al., 2016a), as well as of chronic constipation (Bravo et al., 2011; Ding et al., 2018; Tian et al., 2017) and refractory IBS (Desbonnet et al., 2010; Zoller et al., 2015), although the relative success is questionable given current data (Halkjaer et al., 2018).

AJ. Pain Disorders

A common theme throughout this review is that the microbiota can communicate through neural, endocrine, immune and neuropeptide/neurotransmitter systems, along the gut-brain axis. This also likely holds true for pain response. Facilitation or inhibition of pain processing is mediated at a central level, with ascending afferents from the viscera (including the gut) mediated through the spinal cord as a consequence of primary afferent nociceptor activation, and microbial inflammatory mediators, proteins, and peptides all contributing to the manifestation of pain.

Crudely, pain types can be categorized as nociceptive pain, inflammatory pain (which is associated with tissue damage and the infiltration of immune cells) or pathological pain, which is a disease state caused by damage to the nervous system or by its abnormal function (examples including neuropathic pain, fibromyalgia, migraine and headache) (Woolf et al., 1998). Within these categories, the pain can be further sub-characterized as somatic (skin and deep tissue) or visceral (relating to internal organs). While the anatomical pathways and signaling mechanisms involved in somatic/musculoskeletal pain (skin and deep tissue) and responses to acute nociceptive insults and acute inflammatory pain are relatively well defined, the mechanisms underlying visceral, neuropathic and chronic pain and their treatment are proving a difficult target for therapeutic intervention.

Much of the evidence for gastrointestinal microbiota in pain response has focused on nociceptive disorders of the gut (Holzer et al., 2017; Pusceddu and Gareau, 2018), in particular, inflammatory pain disorders including *C. difficile* infection and IBD, and FGIDs including IBS (see **Section IX. L**). Chronic visceral pain is one of the predominant symptoms of FGID and IBD. It is apparent that both involve centrally and peripherally regulated mechanisms and are therefore often referred to as disorders of the gut-brain axis. However, it is as yet unclear how, or to what extent microbiota that are confined to the gastrointestinal tract can influence visceral pain behavior associated with FGIDs (Moloney et al., 2016; Rea et al., 2017) or IBD (Holzer et al., 2017).

A number of diagnostic studies have determined an altered GI microbiota profile in patients with chronic or recurrent visceral pain, including inflammatory pain in IBD (Conte et al., 2006; Frank et al., 2007; Manichanh et al., 2006) and IBS (Carroll et al., 2012; Jeffery et al., 2012b; Kassinen et al., 2007; Matto et al., 2005; Noor et al., 2010; Shankar et al., 2015; Simren et al., 2013). A common finding across these studies is a decreased relative abundance of the genera Bifidobacterium and Lactobacillus, and increased Firmicutes:Bacteriodetes ratios at the phylum level (Clarke et al., 2012a). The correlational nature of these cross-sectional studies means it is unclear whether these microbiota changes are causative of the nociceptive/inflammatory response, or whether the altered microbiota profile occurs in response to tissue injury or inflammation in the host.

Inflammatory Pain

While antibiotics including metronidazole, vancomycin or fidaxomicin remain first line treatment for *C. difficile* infection, FMT is medically accepted as a highly successful procedure for the eradication of infection

and associated symptoms including abdominal pain (Culligan and Sleator, 2016; Smits et al., 2016). A recent review (Basso et al., 2018) and metadata analysis (Paramsothy et al., 2017) captures the efficacy of microbial-based treatments including probiotic treatments, and FMT in the treatment of IBD. FMT was reported as having >50% clinical remission in some studies while having < 50% clinical remission in others. While probiotics were efficacious in some but not all *C. difficile* infection studies where pain and intestinal discomfort were key comorbidities.

IBD is a chronic, relapsing and remitting painful inflammatory disorder of the gastrointestinal tract comprising ulcerative colitis and Crohn's disease. A recent review has captured the efficacy of FMT in the treatment of IBD (Levy and Allegretti, 2019) with studies reporting 20-33% clinical remission in pain in ulcerative colitis, reduction in pain index in 50-75% Crohn's disease individuals, and mixed effects 0-80% in pouchitis. To date, there are no probiotics demonstrating efficacy in the treatment of Crohn's disease (Knox et al., 2019) while for ulcerative colitis there mixed reports of efficacy of probiotics, with VSL#3 possibly having effect in prevention of relapse in quiescent ulcerative colitis (Derwa et al., 2017). Similarly, in pouchitis, some probiotic interventions were reported as effective or ineffective (Knox et al., 2019) in prevention or alleviation of symptoms.

Arthritic pain is also associated with inflammation. Despite evidence for a role for microbiota, in particular *Prevotella copri* in untreated new-onset rheumatoid arthritis patients (Human Microbiome Project, 2012; Qin et al., 2010; Scher et al., 2013) and evidence from animal studies (Maeda et al., 2016; Scher et al., 2016) human studies are only now being undertaken to investigate the effects of FMT in arthritis (Kragsnaes et al., 2018) and the limited randomized control trials and relatively low participant numbers in probiotic studies have not yielded any clear consensus to the efficacy of probiotics in arthritis (Lowe et al., 2018a).

Visceral Pain

Despite the preclinical evidence for a role for gut microbiota in visceral pain, clinical studies remain inconclusive with a large 'non-responder' population observed in many probiotic and FMT trials. A good example is provided by the range of therapeutic responses to the somewhat controversial technique of FMT from healthy donors to patients with FGIDs. In one study involving patients with IBS (Borody et al., 1989), FMT was effective in 36% of the patients, mildly improved discomfort in a further 16% and was non-effective in the remaining 47%. In a recent double-blind, randomized, placebo-controlled parallel group study design (n=90), FMT was shown to alleviate IBS symptoms three months after transplantation although this was not apparent 12 months after transplantation. Further clinical trials and case studies have utilized FMT for the alleviation of chronic constipation (Andrews and Borody, 1993; Cao et al., 2017; Ding et al., 2018; Tian et al., 2017), refractory IBS (Holvoet et al., 2017; Pinn et al., 2015), and the pain-component of IBD (Angelberger et al., 2013; Bennet and Brinkman, 1989; Kellermayer et al., 2015; Moayyedi et al., 2015; Rossen et al., 2015) with varied success. The efficacy of FMT and probiotic supplementation in the treatment of visceral pain is synthesised in a recent review (O'Mahony et al., 2014).

Neuropathic and Pathological Pain

There is a sparsity of microbiota-related research on many pain types that lack a clear causal localized insult including diabetic neuropathy, stroke-related pain, cancer pain, migraine and headache, or MS-related pain. One case study reported an improvement in diabetic neuropathy following FMT (Cai et al., 2018). Another study reported an improvement in post-chemotherapy abdominal pain following probiotic treatment in colorectal cancer (Osterlund et al., 2007), an event that is caused by chemotherapy-induced gastrointestinal toxicity of the gut microbiome-host immune system (Secombe et al., 2019). Clinical studies have reported a moderate reduction in number, duration and/or intensity of migraine events with probiotic administration (de Roos et al., 2017; Sensenig et al., 2001), while individuals suffering from fibromyalgia, a chronic widespread muscle and joint pain disorder, had no alleviation of pain following probiotic administration (Roman et al., 2016).

Preclinical evidence for a role of microbiota in pain response

GF mice exhibit a blunted response to inflammatory pain (Amaral et al., 2008). When reared in an SPF environment, SKG mice - an animal model of spontaneous Th17-cell dependent arthritis -remained healthy until exposed to zymosan, a fungal β-glycan (Yoshitomi et al., 2005). Similarly, antibiotic-induced depletion of the microbiota decreased visceral pain responses elicited by intraperitoneal acetic acid injection or intracolonic capsaicin infusion in mice (Aguilera et al., 2015). On the other hand, GF animals exhibit an exaggerated response to visceral pain in the CRD model (Luczynski et al., 2017), while antibiotic administration in early postnatal life or in adulthood has been shown to increase susceptibility to CRD in adult rats (Hoban et al., 2016a; O'Mahony et al., 2014). In a seminal FMT study where fecal matter from IBS patients characterized by hypersensitivity to CRD was transplanted to GF rats, an exaggerated response to CRD was observed in the recipient animals (Crouzet et al., 2013), further fueling the gathering interest in the role of the gut microbiota in visceral pain. Together, these findings suggest that depletion of the gut microbiota may be beneficial in reducing sensitivity to inflammatory, but not mechanical, nociceptive information.

There is evidence for positive modulation of pain responses to both inflammatory and mechanical stimuli through probiotic administration (although evidence for prebiotic effects is limited) (Kannampalli et al., 2014; Larauche et al., 2012). *B. infantis* 35624 (McKernan et al., 2010), *L. paracasei NCC2461* (Verdu et al., 2006) and *L. reuteri* (Kamiya et al., 2006) have all been shown to be effective in blunting nociceptive responses to CRD in naïve rodents. Probiotics have also been successfully used to prevent *stress-induced* exaggeration of the pain response to CRD in the maternal separation model of early-life stress (specifically using *L. paracasei* NCC2461 in mice and VSL#3 in rats) (Distrutti et al., 2013; Eutamene et al., 2007) and in adults exposed to restraint stress (using *B. lactis* CNCM I-2494) (Agostini et al., 2012). Similarly, different probiotic species have been shown to ameliorate visceral hypersensitivity to CRD in a rat model of colitis, perhaps through protective effects on intestinal barrier function (restoration of barrier integrity and tight junction protein levels) and/or reductions in circulating inflammatory cytokines (Johnson et al., 2011; Laval et al., 2015; Martin et al., 2016). Finally, prophylactic administration of the probiotic mix VSL#3 suppressed visceral hypersensitivity induced by inflammation via intracolonic instillation of 4% acetic acid (Dai et al., 2012).

While such studies implicate the microbiota in alleviating certain symptoms associated with GI discomfort or pain sensitivity, further research is needed to establish whether FMT results in long-lasting changes in microbiota composition or immune, endocrine, inflammatory or neurotransmitter systems. Further double-blind, randomized control trials would also clarify the effectiveness of FMT in the treatment of FGIDs and potentially provide insight into the reasons for individual differences in treatment response. At the level of the gut, the sensitization of primary afferent nociceptors is thought to lead to visceral hypersensitivity. A number of different receptor types are involved in the process of peripheral sensitization including the transient receptor potential channel (TRPV) family, proteinase-activated receptors, CCK receptors, 5-HT receptors, cannabinoid receptors, as well as an array of ion channels including ATP-gated ion channels, voltage-gated sodium and calcium channels, acid-sensing ion channels and pH-sensitive receptors (Akbar et al., 2009; Vermeulen et al., 2014). A range of physiologically active agents including substance P, glutamate, aspartate, vasoactive intestinal peptide, CCK, somatostatin, calcitonin gene-related peptide and galanin are released from nerve terminals of the visceral primary afferents of the gut to propagate the nociceptive signal to second-order neurons at the dorsal horn of the spinal cord.

There are many potential mechanisms by which the GI microbiota could activate these receptor systems or agents either directly or indirectly. These include local immune-mediated events at the mucosal-epithelial interface during infection, inflammation and autoimmunity (Cassel et al., 2008; El Aidy et al., 2014; Kamada et al., 2013b; Mazmanian et al., 2005; Round and Mazmanian, 2009), or through other chemical messengers including formyl peptides (Husebye, 1997), proteases (Cenac, 2013; Vergnolle, 2009) and PUFA release (Cenac et al., 2015), SCFA production (Cummings and Macfarlane, 1997), neurotransmitter and neuropeptide release (Lyte, 2014) or hormone secretion (Cani et al., 2013; Cani and Knauf, 2016). Microbially-derived biomolecules involved in vasoconstriction could potentially contribute to migraine development. Evidence suggests that the gut microbiota can also stimulate the release of the body's endogenous pain-suppressing compounds including opioids from innate neutrophils and monocytes (Boue et al., 2014), endocannabinoids from colonic tissue (Muccioli et al., 2010), as well as other pain modulators including monoamines (Oleskin and Shenderov, 2016).

AK. Parkinson's disease

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by tremor, rigidity of movement and distinctive gait. Motor impairment and characteristic brain pathology do not present as symptoms until quite an advanced stage of the disease. By this time much of the dopaminergic neurons in the substantia nigra, cells responsible for motor control, have been lost or have degenerated axons (Cheng et al., 2010). Recent evidence from a number of labs (Bedarf et al., 2017; Hasegawa et al., 2015; Hill-Burns et al., 2017b; Keshavarzian et al., 2015; Sampson et al., 2016; Scheperjans et al., 2015; Unger et al., 2016) propose a relationship between the complexity and diversity of the microorganisms that inhabit our gut and PD. Indeed, even an appendectomy was recently seen as a potential prophylactic for PD initiation (Killinger et al., 2018). These studies suggest that, along with an altered GI microbiota profile, a shift to a pro-inflammatory state occurs, with possible detrimental effects in the gut and brain (Perez-Pardo et al., 2018). This supports the frequently observed occurrence of functional GI symptoms such as constipation which often

occur prodromal, years before motor symptoms emerge (Felice et al., 2016; Poewe, 2008). Fifteen years ago, it was first postulated that the etiology of PD might begin in the gut (Braak et al., 2006). A widely used staging tool for PD, the Unified Parkinson's disease Rating Scale (UPDRS), uses semi-quantitative descriptors of motor impairments, but additionally contains measures of non-motor symptoms, including gut effects, reflecting the common occurrence of gut dysbiosis in the disease. Preclinical studies have provided further evidence that microbiota may be causally related to PD symptomatology and pathophysiology, whereby FMT from parkinsonian patients into GF mice overexpressing the PD-linked protein α-synuclein resulted in two hallmark symptoms of PD: motor deficits and neuroinflammation (Sampson et al., 2016), suggesting that distinct microbes are associated with PD. It was notable that symptoms improved when the mice were treated with antibiotics. Altogether, a role for gut microbiota in PD in the initiation and progression of PD seems more and more compelling (Dinan and Cryan, 2017; Perez-Pardo et al., 2017).

An aggregation of the protein α-synuclein in the brain is a hallmark of PD pathology. This has been seen in the mucosal and submucosal nerve fibers and ganglia of PD patients (Forsyth et al., 2011; Hilton et al., 2014). There is also preclinical evidence suggesting that α-synuclein in the gut can transport to the brain via the vagus nerve (Holmqvist et al., 2014), known to be the main conduit for signals from the gut to the brain (see **Section IV. A**.). α-synuclein may exert its effects via microbial influence, or via prion-like translocation to the brain, and may act as a store for pathogenic forms of α-synuclein, increasing the risk of PD development (Killinger et al., 2018). Further, α-synuclein aggregation appears to be modulated by the gut microbial metabolite LPS, a well-characterized interaction associated with this alternative pathway of PD progression (Bhattacharyya et al., 2019). Epidemiological studies have shown that truncal vagotomy in Danish and Swedish patients is protective against PD (Liu et al., 2017a; Svensson et al., 2015). Somewhat ironically, the utilization of vagotomy was stopped when it was discovered that peptic ulcers were caused by *Helicobacter pylori* and could be treated with antibiotics. Further, there is also evidence linking *H. pylori* infection to the development of PD symptoms through degenerating dopaminergic neurons in the brain (Dobbs et al., 2016). Intriguingly, eradication of *H. pylori* has been shown to enhance the onset time of levodopa (first line pharmacological treatment for PD symptoms) while also improving, rigidity, walking ability and tremor (Camci and Oguz, 2016; Hashim et al., 2014).

The original work describing alterations in gut microbiota profile compared PD patients to healthy controls (Scheperjans et al., 2015) and paved the way for further studies on gut microbiota profile in PD. The PD cohort were sampled at a median of 5 years from the appearance of motor symptoms. The authors found that Provotellaceae was significantly reduced in the PD patient cohort, which was unrelated to constipation measures. Furthermore, there was an increased abundance of *Enterobacteriaceae*, which was positively associated with increased levels of postural instability and gait disturbance. A valuable study of gut microbiota from treatment-naïve PD patients (Keshavarzian et al., 2015), also described differences in gut microbiota composition between PD patients and healthy controls. Bacteroidetes, Proteobacteria, and Verrucomicrobia were higher in PD fecal samples at the phylum level, and putative pro-inflammatory bacteria were present at higher abundance at the genus level in the PD samples. They described an association between duration of PD and microbiota profile, although no correlation was found with disease severity, making it difficult to determine if the noted changes were causative or correlative. Another study focused on 19 specific groups/

genera/species and determined that the number of Lactobacillus was higher in the fecal samples of PD patients, while *C. coccoides* and *B. fragilis* groups were lower than that of healthy controls (Hasegawa et al., 2015). This group also attempted to model the disease duration using the microbiota data and observed that increased *L. gasseri* and decreased *C. coccoides* correlated with disease duration, albeit not with constipation levels, which historically correlate with disease duration in PD. An altered microbiota profile in PD was confirmed in another study, where a defined number of bacteria were quantified using PCR (Unger et al., 2016).

Utilizing current metagenomic shotgun analysis techniques, one group discovered that Verrucomicrobiaceae and Firmicutes were increased and Prevotellaceae and Erysipelotrichaceae decreased in a PD patient cohort, who were diagnosed within the previous year and were L-DOPA-therapy naïve (Bedarf et al., 2017), although other concomitant medications were in use. Importantly, key microbial species differences were identified between the PD and control groups, and the authors were able to model PD status using six of the taxa. Further, the effect of 39 potential confounders, including PD medications, were examined in an exciting recent study using a larger cohort of participants (197 PD patients and 130 healthy controls) (Hill-Burns et al., 2017a). This robust study determined that there is a large effect of PD medication on the microbiota profile. The study also confirmed that PD status alone was responsible for significant alterations in gut microbiota. Findings of gut microbe compositional differences in PD have more recently been confirmed in a Chinese population, with the genera Clostridium IV, Aquabacterium, Holdemania, Sphingomonas, Clostridium XVIII, Butyricicoccus and Anaerotruncus found to be increased in PD patients compared to matched controls, and a negative correlation of Escherichia/Shigella with disease duration (Qian et al., 2016). Finally, a study which also took into account a cohort of a presumptive prodromal PD state, namely Idiopathic Rapid Eye Movement Sleep Behavior Disorder, which has a high conversion rate to PD, showed changes in gut microbe composition, which were very similar to the PD cohort, and significantly different from healthy controls (Heintz-Buschart et al., 2018). This offers a tantalizing prospect of being able to utilize gut-microbial profiling as a biomarker for PD in the future. Furthermore, specific operational taxonomic units were associated with both motor and non-motor symptoms, as well as depressive co-morbidities (Heintz-Buschart et al., 2018).

Of note, samples for these human studies were entirely cross-sectional, patients were not followed longitudinally and most of the studies used small cohorts. This strongly identifies a need for larger, prospective and longitudinal studies to confirm these findings and determine whether gut microbiota profile continues to alter throughout disease progression. Interestingly, epidemiological studies of individuals who underwent a full truncal vagotomy for treatment of peptic ulcer disease, which would prevent certain microbiota signals reaching the brain have a diminished risk of Parkinson's disease as they age (Liu et al., 2017a; Svensson et al., 2015). Probiotic interventions to benefit the symptoms of PD are also of interest, with one study published on the benefits of a fermented milk drink containing multiple strains of probiotics in addition to prebiotics in treating constipation in the disease (Barichella et al., 2016). A preclinical study on a nutritional supplement containing prebiotic fibers (FOS and GOS), in addition to other nutrients, has also shown benefit on motor, cognitive and gut symptoms in a mouse model of PD (Perez-Pardo et al., 2017). Much research is needed to help understand how changes in the microbiota can moderate both the non-motor and motor symptoms of Parkinson's disease as well its co-morbidities (Dinan and Cryan, 2017; Lionnet et al., 2018).

AL. Alzheimer's disease and Dementia

Alzheimer's disease is the most common neurodegenerative disorder and the leading cause of dementia. The characteristic brain pathology, including Aβ plaques and hyperphosphorylated tau protein, appears in stages starting in the trans-entorhinal cortex, followed by progression to the hippocampus, and later widespread progression to cortical regions (Braak et al., 1993). The possibility of a microbial origin for the disorder has been discussed for years (Balin et al., 1998; Balin et al., 2008; Friedland, 2015; Itzhaki et al., 2016; Miklossy, 1993, 2016; Zhao et al., 2015) and new evidence continues to emerge in support of this concept (Alonso et al., 2017; MahmoudianDehkordi et al., 2018; Pisa et al., 2018; Pisa et al., 2016). There is now a strong case to be made for a link between pathogenic microbes and the development and progression of AD (succinctly reviewed in (Hill et al., 2014).

Experimental evidence (Soscia et al., 2010) has supported other research identifying the amyloid protein acting as a possible antimicrobial peptide in the brain (Kumar et al., 2016; Stilling and Cryan, 2016). However, from a Koch's postulate perspective, it is ethically difficult to prove that there is an infective etiology to the neuroinflammation, and neurodegeneration observed. The relationship between gut proteins and brain health is receiving much-needed attention. Intriguingly, amyloid-like proteins can be produced by bacteria and have been shown to increase α-synuclein pathology in aged rats and worms (Friedland, 2015). However, much more work is needed to validate such strategies in humans.

While the accumulation of Aβ peptide, and abnormal forms of tau protein, present as traditional indicators of AD (Braak and Braak, 1991) they do not necessarily infer causality. As an infectious agent, viruses are present in the brains of most elderly people and tend to co-localize with areas of AD pathology (Jamieson et al., 1991), and Herpes Simplex Virus 1 (HSV-1) has been associated with AD (Eimer et al., 2018; Itzhaki et al., 1997). Furthermore, examination of the humoral response to the HSV-1 virus revealed that anti-HSV-1 Immunoglobulin M (IgM) antibodies increased the risk of developing AD, whereas IgG antibodies did not, suggesting that persistence of the virus may not play a role in AD but that reactivation of the virus may be contributing to its development (Lovheim et al., 2015). Also, elements of AD are transmissible as shown by inoculation of AD homogenates from humans to the brains of primates and mice (Baker et al., 1994). Further evidence for the role of viruses in AD etiology comes from work showing Aβ deposition and tau aberrations following infection with HSV-1 (Wozniak et al., 2007; Wozniak et al., 2009).

The impact of the microbiota on AD is not restricted to viruses, as bacteria have also been associated with AD pathogenesis. GF APP-PS1 mice (Radde et al., 2006) have a reduced Aβ pathology compared to conventional animals from the same background, indicating that the microbiota may play a role in Aβ biology, and subsequently AD pathogenesis (Harach et al., 2017). Moreover, Aβ has demonstrated anti-microbial properties in murine models of AD (Kumar et al., 2016; Soscia et al., 2010). Many questions remain unanswered regarding the role of viruses and bacteria in the pathogenesis of AD. It appears clear that microorganisms are involved at key nodes of the pathogenic cycle of AD and further research must focus on whether Aβ accumulation is a malfunctioning immune response or a driver of disease (Stilling and Cryan, 2016).

Concerning microbiota composition in individuals with AD, there are two studies describing alterations in the gut microbiota profile of AD patients compared to matched controls (Vogt et al., 2017; Zhuang et al., 2018). The first analyzed samples from 25 AD patients, the majority of whom had very-mild to mild dementia, along with 25 matched controls, and described a reduction in richness and diversity of gut microbiota in the AD samples (Vogt et al., 2017). A variety of taxa were affected, with decreased Firmicutes, increased Bacteroidetes, and decreased *Bifidobacterium* (Vogt et al., 2017). The alterations in microbiota correlated strongly with a pathological load of Aβ and phosphorylated tau species in a subgroup of patients who underwent lumbar puncture for AD markers. The second study also found microbiota composition changes at a variety of taxonomic levels in AD, albeit with some differences from the initial study, including *Bacteroides*, *Actinobacteria*, *Ruminococcus*, *Lachnospiraceae*, and Selenomonadales (Zhuang et al., 2018). A difference between the Firmicutes: Bacteroidetes ratio was also noted in this latest study, which has previously been described in obesity and is intriguing in light of the well-described link between AD and type II diabetes mellitus (Arnold et al., 2018). Furthermore, cognitively impaired but otherwise healthy older adults have alterations in Bacteroidetes, Firmicutes, Proteobacteria, and Verrucomicrobia compared to age-matched cognitively intact individuals (Manderino et al., 2017). Cognitively impaired elderly participants with no definitive AD diagnosis at the time of the sampling, but with a high Aβ load, had a lower abundance of *B. fragilis* and *E. rectale* but higher abundance of *Escherichia/Shigella* compared with both healthy controls and individuals with cognitive impairment but no Aβ pathology (Cattaneo et al., 2017). All microbiota descriptions were observational and not intended to define correlation or causation at this stage.

There are a number of mouse models of AD, which are useful tools for the study of potential microbial-based AD therapeutics. Importantly, GF mice with AD mutations (APP/PS1 model) display markedly diminished Aβ pathology in comparison to conventionally housed AD animals (Harach et al., 2017). This study also described differences between gut microbiota in the aged APP/PS1 mouse model versus wild-type animals. A recent study described how early antibiotic treatment in APP/PS1 mice resulted in reduced Aβ deposition later in life (Minter et al., 2017). Intervention with a *B. breve* strain in an Aβ intracerebroventricular model prevented Aβ-induced cognitive deficits, partially restored memory function, and improved inflammatory status (Kobayashi et al., 2017). A study utilizing the triple transgenic mouse model (3xTg) of AD determined that a probiotic cocktail (a mixture of lactic acid bacteria and bifidobacteria, SLAB51) reduced oxidative stress in the rodent (Bonfili et al., 2018). Another multi-strain probiotic, *containing L. acidophilus, L. fermentum, B. lactis*, and *B. longum* abrogated memory and learning deficits in an intra-hippocampal Aβ model of AD (Athari Nik Azm et al., 2018). Lastly, *L. plantarum* protected against cognitive decline (Nimgampalle and Kuna, 2017). Interestingly, this strain had previously been determined in the 1940s as being able to produce acetylcholine (Stephenson and Rowatt, 1947), the neurotransmitter which is reduced to very low levels in the disease, and upregulation of which comprises the bulk of current pharmacological therapy available for AD.

The translational value of microbiota-gut-brain axis therapeutics for AD patients remains an open question. One randomized, double-blind, placebo-controlled trial of a multi-strain probiotic (a milk drink containing *L. acidophilus, L. casei, B. bifidum,* and *L. fermentum* species) described improvements in the Mini Mental State Exam (Akbari et al., 2016). However, another study showed no improvement in cognition following 12 weeks

of consumption of a multi-strain probiotic, containing Lactobacillus and Bifidobacterium strains, in severe AD patients (Agahi et al., 2018). Much work remains to be done to determine whether targeting the microbiota-gut-brain axis can result in clinically significant improvements that slow or halt AD progression. The current literature provides some preliminary evidence that psychobiotic therapy may one day be considered a possible adjunct therapy in the treatment of AD symptoms, or even in the prevention of disease progression at the prodromal stage. It is possible that an altered gut microbiota profile, or indeed any other biomarker, could more reliably predict AD in the prodromal stages. However, we are still far from this and much work needs to be done to describe better the effects of microbiota-gut-brain axis signaling in AD.

AM. Stroke and Brain Injury

Inadequate blood flow to the brain, resulting in cell death, is a hallmark signature of stroke (Peisker et al., 2017), and a common response to brain injury (Sater et al., 2018). Peripheral and systemic factors, including an enhanced inflammatory response, can worsen outcomes after stroke (Samary et al., 2017; Stoll et al., 1998). Investigating the potential involvement of microbiota-related inflammation in stroke outcomes or recovery is thus a burgeoning area of brain injury research. In a Chinese patient group presenting with stroke or a transient ischemic attack, fecal abundance of three major commensal microbes (*Bacteroides, Prevotella*, & *Faecalibacterium*), were severely depleted, with a concomitant enhancement in abundance of opportunistic pathogens such as *Enterobacter, Megasphaera*, and *Desulfovibrio* (Yin et al., 2015). Moreover, patients presenting with severe stroke had a greater abundance of Proteobacteria over those with milder stroke.

Gut permeability, GI motility, and microbiota composition are all drastically altered in mouse models of stroke (Houlden et al., 2016; Singh et al., 2016; Stanley et al., 2016). Further, FMT into GF mice from a cerebral ischemia model transmitted functional deficits of pro-inflammatory T-lymphocyte (Th1 and Th17 T_{helper} phenotype) trafficking and the ischemia-induced cerebral lesion volume (Singh et al., 2016). Administration of broad-spectrum antibiotics pre-ischemic injury is associated with significantly worse outcomes (Winek et al., 2016). Moreover, antibiotic-induced microbiota dysregulation resulted in a reduction in the trafficking of the pro-inflammatory IL-17^+ $\gamma\delta$ T cells, which was associated with a reduction in IL-17 associated chemokine expression in brain parenchyma, along with reduced neutrophil accumulation and a reduction in infarct volume of the ischaemic site (Benakis et al., 2016). Thus, the gut microbiota appears to influence the magnitude of post-stroke neuroinflammation by modulating intestinal T cell trafficking to the meninges. On the other hand, probiotic supplementation seems to have the potential to benefit brain injury patients; *C. butyricum* had neuroprotective effects in a mouse model of traumatic brain injury (Li et al., 2018a; Sun et al., 2016b). The probiotic treatment was shown to act by protecting intestinal barrier integrity, increasing the expression of cerebral GLP-1R and the secretion of intestinal GLP-1, a 5-HT and appetite-modulating hormone. Although this area needs more investigation, there is great interest in the potential for pre- or probiotic -enriched treatments to mitigate some of the morbidities associated with stroke and cerebral ischemia (Brenner et al., 2017).

AN. Multiple Sclerosis (MS)

Multiple sclerosis (MS) is a CNS related autoimmune disorder defined by accruing motor deficits, blurred vision, and changes in sensibility that appear spontaneously with little to no prodromal signals (Dendrou et al., 2015). Based on the immune etiology of MS, much interest is now focused on possible therapeutic intervention via the gut microbiota (Berer et al., 2011; Tremlett and Waubant, 2018). Remarkably, when fecal matter from MS patients was transplanted into mice, the animals began to exhibit one of the hallmark symptoms of MS: autoimmune encephalomyelitis (Berer et al., 2017; Cekanaviciute et al., 2017). GF mice also exhibited resistance to developing experimental autoimmune encephalomyelitis in a mouse model of MS, which was promoted by gram-positive segmented filamentous bacteria in the gut (Berer et al., 2017; Lee et al., 2011). It was noted that the symptom expression correlated with an increase in relative abundance of *Akkermansia*. This fits with a recent study showing that *A. muciniphila* and *Acinetobacter calcoaceticus* are present in relatively higher abundance in fecal samples from MS patients, (Cekanaviciute et al., 2017). The MS patients also exhibited reduced levels of *Parabacteroides distasonis*, a species associated with anti-inflammatory activity. It appears that the gut microbiota of MS patients has a notable role in the disease expression, which may be amenable to dietary intervention. Future studies with targeted microbiota interventions are needed to validate such a hypothesis. Interestingly, in further support of such a concept is the fact that the manifestation of experimental autoimmune encephalomyelitis has also been linked to diet-induced changes in the microbiota (Libbey et al., 2018).

AO. Obstructive sleep apnea

Obstructive sleep apnea (OSA) is defined as breathing interruptions during sleep due to the collapse of the upper respiratory tract, resulting in sleep disturbances (Randerath et al., 2018). Apneic events cause transient hypoxia, decreased oxygen levels in blood, and hypercapnia, increased carbon dioxide in blood. OSA is highly prevalent in the obese and aged populations and represents a risk factor for many cardiometabolic disorders, such as diabetes mellitus type 2 and hypertension (Franklin and Lindberg, 2015). Nevertheless, the mechanisms connecting OSA and its comorbidities remain elusive. Recent studies have examined if changes in gut microbiota are connected to OSA and associated metabolic disturbances, which have been already linked to modifications in gut microbiota composition (Benedict et al., 2016; Tripathi et al., 2018). Two methods utilized in the examination of this potential relationship are sleep fragmentation, and induction of hypoxia and hypercapnia, both of which are defining characteristics of OSA.

Further evidence comes from a recent rodent study, mice that underwent four weeks of sleep fragmentation displayed changes in gut microbiota composition, including an increase in the Firmicutes: Bacteroidetes ratio (Poroyko et al., 2016), similar to that seen in aging and obesity (Castaner et al., 2018; Xia et al., 2016). Mice that underwent sleep fragmentation also exhibited increased Lachnospiraceae and decreased Lactobacillaceae abundancies, as well as colonic barrier disruption, prompting a rise in peripheral inflammation markers (Poroyko et al., 2016). In a recent study, antibiotic treatment depressed the ventilatory response to hypercapnic stress in awake, responsive animals (O'Connor et al., 2019). Further, FMT also disrupted the gut microbiota composition that was associated with depressed ventilatory responsiveness to hypercapnia. In this instance, both antibiotic treatment and FMT resulted in significant disruptions to brainstem monoamine

neurochemistry, which correlated with the abundance of several bacteria of six different phyla (O'Connor et al., 2019). Moreover, in a recent guinea pig study, chronic intermittent hypoxia (CIH)-induced hypertension which models human sleep apnea was shown to alter gut microbiota richness and composition, brainstem neurochemistry, and autonomic control of heart rate, suggesting modulation of breathing and autonomic homeostasis via the microbiota-gut-brainstem axis (Lucking et al., 2018).

From a translational perspective a human clinical study, two nights of partial sleep deprivation raised the Firmicutes: Bacteroidetes ratio in a cohort of healthy young adults (Benedict et al., 2016), a translationally similar result to that seen in rodents. Both geriatric and pediatric patients suffering from OSA present with elevated blood levels of an immune marker of intestinal barrier disruption, LPS-binding protein (Kheirandish-Gozal et al., 2014; Kong et al., 2018). These indirect impacts on the gut microbiota could potentially trigger downstream pathways, leading to metabolic dysfunction. While other recent work was unable to reproduce such results with their sleep restriction model (Zhang et al., 2017b), OSA-derived hypoxia and hypercapnia resulted in gut microbiota functional and compositional alterations in humans (Moreno-Perez et al., 2018) affecting intestinal molecules such as bile acids, phytoestrogens and fatty acids, the synthesis of which is dependent on gut microbiota (Tripathi et al., 2018). Although the connection between OSA and gut microbiota appears strong using the sleep fragmentation model, it appears that hypoxic state may be integral to the effects of OSA on the gut microbiota. Further research is needed to determine the role of the gut microbiota in OSA.

AP. Epilepsy

Even though there are many studies in GF mice examining neural changes in the key brain regions implicated in epileptogenesis (Cowan et al., 2018; Diaz Heijtz et al., 2011; Hoban et al., 2018; Luczynski et al., 2016a; Luczynski et al., 2016b; Olson et al., 2018; Spinelli and Blackford, 2018), there is a paucity of knowledge on the specific involvement of the microbiota in epilepsy. As referred to earlier, there is a strong link between a ketogenic diet and its effects on microbiota composition (Newell et al., 2016; Xie et al., 2017), a common dietary treatment prescribed to patients with epilepsy (Masino and Rho, 2019). GF mouse research has shown the beneficial effects, as well as dependency on the microbiota, a ketogenic diet can have, where a reduced fiber content diet similar to the FODMAP diet can improve symptoms but also be detrimental to the microbiota (Olson et al., 2018), indicating a potential role for the microbiota as a mediator of epileptogenesis.

AQ. Amyotrophic Lateral Sclerosis (ALS)

ALS is a fatal neurodegenerative motor neuron disease characterized by CNS and systemic inflammation resulting in rapid and progressive loss of peripheral motor functions; most patients die within five years of diagnosis (Zhang et al., 2017c). A lower abundance of butyrate-producing bacteria, associated with gut permeability, has been detected in a murine model of the disorder (Zhang et al., 2017c). However, human studies have thus far failed to find a link between the gut microbiota and disease progression in ALS (Brenner et al., 2018).

AR. Huntington's disease

Huntington's disease is a congenital progressive brain disorder of genetic origins, caused by a dominant mutation in the Huntingtin gene (McColgan and Tabrizi, 2018). Symptoms include progressive motor, cognitive and psychiatric decline, caused by neuronal dysfunction and cell death. Sadly, there are currently no treatment options for Huntington's disease, other than symptom management and pain alleviation. Interestingly, intrinsic and extrinsic environmental factors have been shown to modify progression of the disease (van Dellen and Hannan, 2004). Altered gut microbiota-derived metabolites have been observed in subjects exhibiting early symptoms of Huntington's disease, indicating the possibility for microbiota-based interventions (Kong et al., In Press). Further, recent work highlighted that the lack of a microbiome in a mouse model of HD (BACHD-GF) resulted in changes in corpus callosum myelin thickness and plasticity (Radulescu et al., 2019). Further research is needed to uncover any specific role that the microbiome may play in this disease.

AS. Infections and the Brain

Infections of the CNS have been the one area in medicine that the disciplines of microbiology and neuropsychiatry have converged whether it was in the case of neurosyphilis, a major problem in the 19th and early 20th century (Hackett, 1963; Tampa et al., 2014), or the realization of the cognitive effects of the HIV virus (Watkins and Treisman, 2015; Woods et al., 2009). Infections can be caused by bacterial, viral, fungal or parasitic pathogens and their effects can be devastating (Engelhardt and Sorokin, 2009). Thus, understanding the mechanisms of how brain infections occur will have an impact on how the microbiome could influence the brain. Moreover, the presence of a microbiome within the brain itself is very controversial and much more work is needed in this regard (Servick, 2018).

Pathogens can enter the brain via three main routes. Firstly, pathogens enter the brain via the blood or CSF; under physiological conditions, this passage is prevented by the BBB or the blood-CSF barrier. However, diseases such as endocarditis (Ruttmann et al., 2006) and HIV (Atluri et al., 2015) can result in bacteria or viruses entering the brain. Also, long-term use of steroids and organ transplant can also compromise the BBB and blood-CSF barrier resulting in bacterial translocation (Coureuil et al., 2017). Secondly, direct entry during an ear infection, sinusitis, mastoiditis, and osteomyelitis amongst others, can take place. Lastly, pathogens can enter the brain following skull fracture or traumatic brain injury (TBI). Not every bacterium has the potential to enter the brain and those that do have adapted specific molecular methods to allow translocation. Indeed, TBI itself has been shown to result in an alteration in fecal microbiota (Treangen et al., 2018). While these barriers represent an important obstacle against infection, they also prevent the access of important drugs to the brain. Current and future research must define the exact mechanisms that pathogens use and harness these tactics for improved drug delivery to the CNS.

Bacterial infections of the brain are typically confined to the meninges, three important membranes that enclose the brain and spinal cord (Honda and Warren, 2009). One of the most common bacterial infections

of the brain is bacterial meningitis, usually caused by extracellular pathogens such as *S. pneumonia*, (pneumococcal meningitis) *Neisseria meningitidis* (meningococcal meningitis) and *Haemophilus influenzae*, the most common causes of bacterial meningitis in adults and children worldwide (Heckenberg et al., 2014). Bacteria responsible for meningitis are frequently considered commensals at mucosal surfaces and only pose an infectious threat when they enter the brain via the bloodstream or CSF (Coureuil et al., 2017). Not all bacteria responsible for meningitis have the same tendency to infect the meninges. For example, meningitis is common during meningococcal disease whereas *S. pneumoniae* while capable of causing meningitis is rarely seen in pneumococcal disease (Coureuil et al., 2017). Furthermore, it is clear that bacteria may enter the brain at different sites using different methods, implying that different bacteria employ different techniques to breach the barriers to the brain (Huang and Jong, 2001).

A clearer picture of how the brain is affected by infection is essential to understand the mechanisms by which neurological disease occurs and how the microbiome-gut-brain axis may regulate it. The brain has a specific mechanism in place that have been exploited by bacteria, viruses and parasites, understanding the methods these pathogens use will present a clearer understanding about how outside threats can penetrate the brain and cause devastating disease.

XII. Beyond the "Bacteriome"

Bacteria have long been the primary subjects of microbiota research, but the remaining members within the gut microbiota have begun to garner more interest as their presence not only impacts the consortia of bacteria but also can also directly impact the host. The highest fraction of the gut microbiota are viruses, which outnumber their mammalian and microbial hosts by a large margin; thus, they cannot be ignored. Fungi are found in lower numbers but may impart a large effect on the function of the microbiota and host, particularly in immunocompromised individuals. The virome (collection of viruses) and the mycobiome (collection of fungi) within the microbiota, each serves complex roles, which we will now explore.

The Virome

The gut virome is comprised of viruses capable of infecting host mammalian cells, as well as eukaryotic, bacterial, fungal, and archaeal cells. Viruses that infect bacteria (ie. bacteriophage or simply phage) predominate in both number and diversity in the virome. Characterizing the virome has proven challenging as the phage community contains divergent genomes, and retain no conserved gene region utilizable for identification, similar to the bacterial 16S rRNA genes. Some phage in the gut are lytic (virulent) where they hijack host cell transcription/ translation machinery to generate many more phage components before lysing the host cell membrane and releasing phage particles into the local environment. However, more commonly phages in the gut are lysogenic, where they incorporate their DNA into the plasmid or genome of the host cell and replicate along with the host over time. In addition to replicating with their host through successive divisions, lysogenic phage can also drive diversification and evolution by imparting new genes to their bacterial host that can increase substrate utilization range, induce virulence, protect from phage superinfection, provide resistance against antimicrobials, and many other positive and negative growth factors (Manrique et al., 2017). The

most prolific phages in the gut are temperate phages and can be both lytic and lysogenic, whereas virulent phages are obligately lytic (Foca et al., 2015; Kim and Bae, 2018). Temperate phages can transition between lytic and lysogenic states depending on environmental factors. For example, lysogenic phages can become lytic when environmental stressors cause DNA injury (Monk and Kinross, 1975) or loss of host fitness (Rokney et al., 2008), such as with antibiotics (Cowlishaw and Ginoza, 1970), oxidation (Figueroa-Bossi and Bossi, 1999)Animal/*microbiology</keyword><keyword>Salmonella Phages/drug effects/genetics/growth & development/*physiology</keyword><keyword>Salmonella typhimurium/drug effects/genetics/pathogenicity/*virology</keyword><keyword>Superoxide Dismutase/genetics</keyword><keyword>Virulence/genetics</keyword><keyword>Virus Activation/drug effects</keyword></keywords><dates><year>1999</year><pub-dates><date>Jul</date></pub-dates></dates><isbn>0950-382X (Print, bacterial conjugation (Wollman et al., 1956), and heat (Rutberg, 1973). The lytic and lysogenic lifestyles of viruses make it difficult to unravel many of the potential interkingdom interactions within the gut microbiota, but the intrinsic predation of bacteria by bacteriophages drives adaptation and diversification for bacterial resistance and phage infection (De Sordi et al., 2019). Since the phage population is dependent on available hosts, extrinsic factors that can alter bacterial community dynamics can also shape the phage population. A bloom of one strain of bacteria will increase phage diversity targeting predation on that bacterial group, thus increasing bacterial diversity through kill-the-winner dynamics (also described as the Red Queen effect and in the Lotka-Volterra model dynamics (Rodriguez-Valera et al., 2009; Thingstad and Lignell, 1997)). This is exemplified in IBD where reduced bacterial diversity leads to increased phage expansion and diversification (Lepage et al., 2008; Norman et al., 2015). Interestingly, human phage community profiles show low temporal intrapersonal diversity, but high interpersonal diversity (Reyes et al., 2010), further complicating the picture.

Phages in the gut environment are capable of playing a large role in shaping the microbiota as the gut ecosystem is suggested to be one of the densest phages habitats in the world, where up to 10^{15} phage particles have been estimated in the GI tract (Dalmasso et al., 2014; Lepage et al., 2013; Mills et al., 2013). Identification of phage capable of utilizing quorum sensing molecules of their bacterial host has shown that phage are capable of making lysis-lysogeny decisions dependent on communication systems of bacteria that may infer bacterial growth trajectory (Silpe and Bassler, 2019). The most commonly studied and identified phages in the gut are of the order Caudovirales within the families Siphoviridae, Podoviridae, and Myoviridae (Lepage et al., 2008). More recent studies have identified crAss-like Bacteriophages as the most abundant viruses in the gut, where indirect evidence suggests they primarily infect bacteria of the genus Bacteroides (Dutilh et al., 2014; Shkoporov and Hill, 2019; Yutin et al., 2018). Phage are similarly ubiquitous in feces, reported at a concentration of approximately 10^8 per gram and equaling the number of bacteria, further indicating their importance for consideration during FMT (Kim et al., 2011)Kyung Hee University, 1 Hoegi-dong, Dongdaemun-gu, Seoul 130-701, Republic of Korea.</auth-address><titles><title>Diversity and abundance of single-stranded DNA viruses in human feces</title><secondary-title>Appl Environ Microbiol</secondary-title></titles><periodical><full-title>Appl Environ Microbiol</full-title></periodical><pages>8062-70</pages><volume>77</volume><number>22</number><edition>2011/09/29</edition><keywords><keyword>*Biodiversity</keyword><keyword>Centrifugation, Density Gradient</keyword><keyword>Cluster Analysis</keyword><keyword>DNA Viruses/*genetics/*isolation & purification</keyword><keyword>DNA, Single-Stranded/*genetics/isolation & purification</keyword><keyword>DNA, Viral/*genetics/isolation & purification</keyword><keyword>Feces/*virology</keyword><keyword>Filtration</keyword><key-

word>Humans</keyword><keyword>Nucleic Acid Amplification Techniques</keyword><keyword>Phylogeny</keyword><keyword>Sequence Analysis, DNA</keyword><keyword>Sequence Homology, Nucleic Acid</keyword><keyword>*Viral Load</keyword></keywords><dates><year>2011</year><pub-dates><date>Nov</date></pub-dates></dates><isbn>1098-5336 (Electronic. Interestingly, FMTs that have had the bacterial fraction filtered out have been shown to result in similar treatment efficacy and resolution of *C. difficile* infection (Ott et al., 2017; Zuo et al., 2018). In individuals with *C. difficile* infection that were successfully treated with FMT, there was stable engraftment of bacteriophages from donors to recipients for up to 12 months following treatment (Draper et al., 2018). This long-term colonization is evidence that phages play an active role in the microbiota since inactive phages would be quickly washed out.

Elucidation of safe and effective phage therapy has been a desired paradigm for decades, and in the age of increasing antibiotic resistance, is of growing importance. The utmost care must be taken regarding the effects that phage therapy can have longitudinally on the mammalian host directly, or indirectly via the gut microbiota. One recent study showed that phage cocktails generated from a number of bacterial isolates resulted in increased intestinal permeability in rodents (Tetz and Tetz, 2016; Tetz et al., 2017). Further, it has been demonstrated in rodent models that phages are capable of crossing the GI barrier following gavage (Duerr et al., 2004; Hamzeh-Mivehroud et al., 2008). Additionally, phages have been shown to cross through epithelial cell layers via transcytosis, allowing access to various regions in the body that are usually considered sterile (e.g. blood, lymph, organs; (Nguyen et al., 2017). Phages were not believed to directly invoke an immune response in humans (Sarkar et al., 2016), but they can be removed through innate immunity mechanisms (Merril, 2014), and play an important role in antibacterial innate immunity. A recent study showed that bacteriophage proliferation is linked to intestinal inflammation and colitis in a preclinical IBD model, suggesting that phage can modulate varying effects on the host including TLR9 mediated IFN-γ immune response specific to Bacteroides bacteriophages and phage DNA (Gogokhia et al., 2019). The 'bacteriophage adherence to mucus' model proposes that phage provide antibacterial immunity to the host through mucin glycoproteins binding with proteins exposed on phage capsids. Therefore, concentrated phage in the mucus layer may provide a defense system against bacteria for the epithelial cells below (Barr et al., 2013). Since phages are capable of modulating proliferation of their bacterial hosts, sculpt microbiota composition, and modulate inflammation in the mammalian host, their effects on other aspects of human health and cognition will continue to be a burgeoning new area of research for years to come.

The Mycobiome

Fungi resident in the gut mycobiome are less prevalent than both their bacterial and viral counterparts, and like viruses, their role in the gut microbiota is not as well understood as bacteria. Fungi in the GI tract have been reported to comprise 0.001-0.1% of the total population (approximately a billion organisms; (Huseyin et al., 2017), and about 10^6 / gram in stool (Bojanova and Bordenstein, 2016)). In a number of studies many members of the mycobiome have been reported, yet few would be considered common, leading some researchers to question the role, and true colonization of the gut by fungi, since the presence of most members in stool can be explained by oral colonization and transient passage through the gut in a healthy individual (Auchtung et al., 2018; Hallen-Adams and Suhr, 2017). This perspective argues that gut colonization by fungi could be indicative of a diseased and immunocompromised individual, which could certainly help

explain why some of the most common members identified (*Candida*, *Malassezia, Geotrichum, Cladosporium*) are also opportunistic pathogens. Other fungi unable to colonize such as *Saccharomyces, Aspergillus,* and *Penicillium,* are common either in diets or the environment and are expected to impact the ecology of the myco- and microbiota (Hallen-Adams and Suhr, 2017). In IBD, fungal communities have been described as having increased diversity and a varied composition compared to the mycobiomes of healthy individuals (Ott et al., 2008). In one study in both humans and rodents, a change in fungal composition was correlated with increased visceral hypersensitivity, supporting the notion that IBS related visceral hypersensitivity may be treated with antifungal medication (Botschuijver et al., 2017). Given the potential for interaction of nociceptive sensory pathways by the mycobiome, fungi may well play a larger role in the gut-brain axis than previously thought. Similar to the other less frequently studied microbes in the gut, a gold standard approach for culture-independent metagenomic analysis is lacking. Undoubtedly, more work is needed to better understand the presence and purpose of fungi in the gut.

XIII. Conclusions

Expansion of the Gut-Brain Axis into Microbiota-Gut-Brain Axis or Diet- Microbiota-Gut-Brain Axis

Understanding how gut microbes influence gut-brain axis communication has been the subject of significant research over the past decade. There is a growing effort to dissect out the mechanisms of this communication at all nodes of the axis. It is now widely believed that the gut microbiota is critically important for the appropriate development and maintenance of brain function. Moreover, as outlined above there is accumulating evidence from both animal and clinical studies implicating the microbiota in a variety of psychiatric, neurological and neurodegenerative diseases. However, it is still very much early days in this field and caution is needed in over-interpreting such studies. Whether changes in the microbiota are central to the pathophysiology of at least some psychiatric and neurological disorders is currently unproven, though the subject of considerable speculation. To date, IBS is the only clinical condition where targeting the microbiota has been shown to result in clinical improvement in placebo-controlled trials. There also remain many unanswered questions regarding psychobiotics, with much work required to test optimal dosing, strain, and timing in therapeutic applications. It will be important for the field to move away from just correlative analysis towards prospective longitudinal studies, causative and mechanistic analyses, and larger scale trials of potential therapeutic approaches. Without doubt, studies across a wide spectrum of disorders will be available shortly, which is an exciting prospect for the promise of therapeutic applications for the microbiota is great.

One of the big conundrums in microbiota-based medicine is how to define a healthy microbiota. Inter-individual differences in microbiota composition can be great, which makes a “one size fits all” approach to targeting the microbiota challenging. However, it also offers opportunities as the microbiota may be the conduit for effective personalized medicine approaches in the future (but see (Zmora et al., 2018)).

Given the role of diet in modulating the microbiota, we may really be focusing on a diet-microbiota-gut-brain axis in mediating health and disease across the lifespan. Thus, in addition to the quote at the beginning of

this review, Hippocrates was also reported to have said: “let food be thy medicine.” Perhaps a modified version now warrants consideration “let food for your microbes be thy brain medicine.”

XIV. References

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XV.

XVI. Figure Legends

Figure 1. Schematic outlining the myriad of changes recorded in Germ-free mice compared to conventionally housed mice with specific emphasis on neural alterations.

Indicates an increase and signifies a decrease in the relative process.

Figure 2. Sequential schematic illustrating the steps involved in modern bioinformatic analysis of microbiota samples. The process begins with the extraction of a bacterial genome which is sequenced and digitized; upon identification of the species involved, diversity and abundance are analyzed delivering a functional analysis chart and a PCAnalysis plot for reference and inference.

Figure 3. Timeline graph indicating changes in microbial diversity across the human lifespan, from birth through aged, including infancy, childhood, adolescence, and adulthood, accompanied by typical changes in neural development, indicating concomitant neuronal processes occurring during specific stages of life. Blue bar depth means to signify time period where indicated processes are greatest.

Figure 4. Schematic outlining the various known bidirectional pathways of communication between the gut-microbiota and the brain, including hepatic and gallbladder metabolism, immune-modulatory responses, neuronal innervation enteroendocrine and microbial metabolite signaling.

Figure 5. Illustration identifying common factors known to impinge on microbiota-gut-brain activity, including diet, congenital heredity and associated epigenetics, environment, medications, exercise and mode of delivery at birth, as well as the various behaviors known to be affected by microbiota-gut-brain axis perturbation, including cognitive and social behaviors, stress, fear and food intake.

Figure 6. An outline illustrating the variety of disease and disease processes the microbiota are currently implicated in; examples include psychiatric and neurodegenerative disorders, pain, stress, IBS, stroke, addiction and obesity.

XVII. Tables

Table 1: Model organisms currently utilized for the study of the microbiota-gut-brain axis.

Table 2: Germ-free animal studies of the microbiota-gut-brain axis, categorized by model organism.

Table 3: Antibiotic studies of the microbiota-gut-brain axis, categorized by model organism.

Table 4: Prebiotic studies of the microbiota-gut-brain axis, categorized by model organism.

Table 5: Probiotic studies of the microbiota-gut-brain axis, categorized by model organism.

Table 6: Tools used in the analysis of the gut microbiome

Table 1: Model organisms currently utilized for the study of the microbiota-gut-brain axis.

Species	Influence on brain & behavior	Intervention	Advantages	Disadvantages	Ref.
Humans (*Homo sapiens*)	Modulation of stress hormones secretion, stress perception, autism-related behavior, and cognition. Implicated in Alzheimer's disease, Parkinson's disease, and stroke.	Probiotic	-Ability to report definitive behavioral effects of microbiota modulation.	-High degree of genetic variability, confounding covariates (environment, diet, lifestyle), recruitment and sample size.	(Allen et al., 2016; Finegold, 2011; Jiang et al., 2015; Kelly et al., 2016; Sampson et al., 2016; Tomova et al., 2015)
Chimpanzee (*Pan Troglodytes)*	Composition of microbiota is highly influenced by social interactions.	Microbiota sequencing	↑ genetic similarity to humans.	Confounding covariates influence microbiota composition: captivity versus the wild, sympatric speciation and social interaction.	(Gilbert, 2015; Moeller et al., 2016; Szekely et al., 2010; Uenishi et al., 2007)

Mouse (*Mus musculus*)	Influences neurophysiology and behavior: cognition, sociability, anxiety, depression-related, addiction and reward, and eating.	Prebiotic Probiotic Antibiotic Diet FMT GF	-Control for age, sex, diet, treatment compliance. -Vagotomy, DREADDs optogenetics. -Gene specific gene manipulation/ specific genetic mouse models.	↓Translatability to humans -Behavior readouts are different from that seen in humans.	(Bravo et al., 2011; Buffington et al., 2016; de Theije et al., 2014b; de Theije et al., 2014c; Desbonnet et al., 2014; Desbonnet et al., 2015; Erny et al., 2015; Hsiao et al., 2013; Poutahidis et al., 2013; Robertson et al., 2017a; Savignac et al., 2014)
Rat (*Rattus Norvegicus*)	Similar to mouse, Unique animal model of early life stress: maternal separation Brain and behavior.	Prebiotic Probiotic Antibiotic Diet FMT	-Control for age, sex, diet, treatment compliance. -More complex behavior than mouse. -Vagotomy, DREADDs optogenetics.	↓Translatability to humans -Behavior readouts are different from those seen in humans.	(Kelly et al., 2016; O'Mahony et al., 2011; Pusceddu et al., 2015)
Hamster (*Mesocricetus auratus)*	Used in stress studies.	Probiotic Stress	-Control for age, sex, diet, treatment compliance.	-Behavior: live in isolation/ non-social behavior. Less Validation. Prone to developing metabolic disorders.	(El-Ansary et al., 2018; Partrick et al., 2018)

Zebrafish (*Danio rerio*)	Anxiety-related behavior and sociability in zebrafish. Non-mammalian model for validation.	Probiotic antibiotic GF	-Control for age, sex, diet, treatment compliance. -Easily manipulated genome	↓↓Translatability to humans.	(Borrelli et al., 2016; Davis et al., 2016; Wang et al., 2016)
Ants (from the *Lasius* genus)	↑ social - social behavior. Horizontal transmission of microbiota between conspecifics. Dietary intervention. Non-mammalian model for validation.	Diet Infection	-Population-based cooperative and social behavior.	↓↓Translatability to humans. -Difficulties studying in the wild versus controlled laboratory environment.	(Kay et al., 2014; Tragust et al., 2013)
Fruit fly (*Drosophila Melanogaster*)	Enteric bacteria influence on mating behavior. Non-mammalian model for validation.	Probiotic Antibiotic	-Control for age, sex, diet, treatment compliance. -Easy isolation of evolutionarily conserved neurological pathways. -Species-level MGBA testing Easily manipulated genome.	↓↓Translatability to humans. -No adaptive immune system. - GI system is vastly different to that of mammals and humans.	(Chen et al., 2019; Damodaram et al., 2016; Pandey and Nichols, 2011; Sharon et al., 2013)

Table 2: Germ-free animal studies of the microbiota-gut-brain axis, categorized by model organism.

Strain, Sex	Parameter	Behavioral Test, Phenotype	Tissue/ Region	Ref.
Mouse				
BALB/c, ♂	Anxiety Locomotion Transcription	OFT: ↑anxiety-like behavior. Not reversible via colonization. NSF: ↓latency. Differences in miRNA and mRNA expression. Most altered pathway: axon guidance. Few miRNA and mRNA transcript levels restored after colonization.	Hippocampus	(Chen et al., 2017a)
	Anxiety Locomotion	OFT, MB: ↑anxiety-like behavior. ↓spontaneous motor activity. *Brautia coccoides* ↓MB, no effect on locomotion test. *B. infantis* ↓the locomotor activity, no effect on MB.	Brain	(Nishino et al., 2013)
	BDNF NMDARs	↓*Bdnf* ↓glucocorticoid receptor expression. ↓*Nr1, Nr2a* in cortex, ↑*Nr2a* in hippocampus.	Cortex, hippocampus,	(Sudo et al., 2004)
	Brain Size	Brain weight did not ↑with age as it did in SPF mice.	Brain	(Kawase et al., 2017)
♀	Scrapie pathogenesis	No differences with IC inoculation, but mice lived longer.	Brain	(Wade et al., 1986)
BALB/c and C57BL/6J, ♂	BBB	↑BBB permeability, ↓tight junction proteins. Partially reversed by colonization of certain species or SCFA.	BBB	(Braniste et al., 2014)
C57BL/6	Myelination	↓Expression of myelin basic protein.	Brain	(Lu et al., 2018)
C57BL/6j ♂ and ♀	Microglia	Time and sex-specific changes in colonization, chromatin accessibility.	Neocortex	(Thion et al., 2018)
♂	Social behavior (sociability, social novelty, reciprocal social interaction)	Monocolonization with *L. reuteri* reversed social deficits.	Vagus Nerve	(Sgritta et al., 2019)
♀	EAE	More resistant to EAE than control mice. This was reversed via microbiota colonization.	CNS	(Lee et al., 2011)
♂	Fear extinction/ retention Transcription	Fear retention: ↓freezing/impaired memory. ↑ plasticity IEG. Unique transcriptional response to fear stimulus. Reversed with post-weaning colonization.	Amygdala	(Hoban et al., 2018)

	Transcription BDNF	↓*Gcg* in brainstem, ↑ transcription of obesity producing neuropeptides in hypothalamus. ↓ Obesity suppressing peptides in hypothalamus incl. ↓*Bdnf.*	Hypothalamus and brainstem	(Schele et al., 2013)
	Social Preference	3 Chamber: Reciprocal Interaction: ↓sociability, social novelty, social interaction. Reversed via colonization, or with just *L. reuteri.*	Brain	(Buffington et al., 2016)
Chinese Kun Ming (KM), ♂	Anxiety	OFT: ↑anxiety-like behavior.	Brain	(Huo et al., 2017)
C57BL/6J & C57BL/6N	Neurogenesis	↓ BrdU incorporation: ↓proliferation. Colonization via co-housing with SPF mice.	SGZ of hippocampus	(Sawada et al., 2018)
♂ and ♀	Anxiety BDNF	TST, step-down, LD: ↓anxiety-like behavior following maternal separation in LD test, ↑ Step-down, ↓immobility in TST. ↓*Bdnf.* Partial rescue of phenotype via colonization in maternal separation stress, sex-dependent.	Hippocampus, Gut neurons	(De Palma et al., 2015)
C57BL/6 NarI, ♂	Anxiety Locomotion	EPM, FST, OFT: ↑anxiety-like behavior. No change via FST. ↓locomotor activity relative to probiotic group. Reversible via *Lactobacillus plantarum* PS128.	Striatum	(Liu et al., 2016a)
Chinese Kun Ming (KM), ♂	Schizophrenia	FMT from human schizophrenia patients (SCZ). OFT: ↑ activity, ↓ anxiety. FST: ↓ immobility. Exaggerated startle response to high-decibel tones (120 db) in SCZ mice. ↑ Hippocampal GABA. ↑ hippocampal and serum glutamine. ↓ Hippocampal and stool glutamate. Altered cortical GABA, glutamine and glutamate.	Hippocampus PFC	(Zheng et al., 2019)
NMRI, ♂	Anxiety Locomotion Synaptic Activity Transcription	OFT, EPM: ↓anxiety-like behavior. ↑activity ↓ PSD95, synaptophysin expression. ↑NA, DA, 5-HT turnover. ↓*Ngfi-a & Bdnf.* DA D1 receptor: ↑expression in hippocampus, no significant difference in striatum or nucleus accumbens.	Striatum, Cerebellum, Hippocampus, PFC, NAc	(Diaz Heijtz et al., 2011)
Swiss Webster, ♂ & BALB/c	Anxiety	Step-down, light/dark box: no change. ↑ Anxiety after recolonization	Brain	(Bercik et al., 2011a)
Swiss Webster	Anxiety	mRNA dysregulation Somewhat reversible via colonization (not all transcripts)	Amygdala, PFC	(Hoban et al., 2017)
	Neurogenesis	↑Survival of progenitors. Not reversed by microbiota colonization.	SGZ of hippocampus	(Ogbonnaya et al., 2015)

♂ and ♀	Anxiety Social Preference Cog & Memory Locomotion	EPM, OFT 3 Chamber: anxiolytic behavior, sociability deficit and hyperlocomotion in ♀. NOR: memory deficit. Some parameters reversed via early-life colonization with *Bifidobacterium* or complex microbiota.	Brain	(Luk et al., 2018)
	Electrophysiology	No differences in seizure susceptibility.	Brain	(Olson et al., 2018)
	BDNF	↓Brain *Bdnf* levels when compared to ♂ not ♀.	Hippocampus	(Clarke et al., 2013)
	Myelination	↑ Myelination genes regulation, regional and sex-specific differences in gene expression, hypermyelination in PFC.	PFC	(Hoban et al., 2016b)
♀	Anxiety Locomotion	OFT: no effect. EPM, ↓anxiety-like behavior with ↓ *NR2B, 5-HT$_{1A}$* ↑*Bdnf*.	Hippocampus, Amygdala	(Neufeld et al., 2011)
	Anxiety, memory	LDB: no change. ↓BDNF in CA1. ↓c-fos expression after acute stress. NOR, T-Maze: ↓exploration, memory. Reversible with *C. rodentium.*	Hippocampus	(Gareau et al., 2011)
♂	Anxiety Social Preference	OFT: ↓anxiety-like behavior. 3 Chamber: ↑ sociability. ↓*Bdnf.*	Amygdala	(Arentsen et al., 2015)
	Depression	FST, TST, SPT: ↓depressive behaviors and ↑ ΔFosB.	DRN Hippocampus	(Campos et al., 2016)
	Olfactory memory Social Preference/ Cognition Self-Grooming	Social Food Transmission impairment: ↑grooming. 3 Chamber: ↓sociability and social novel preference. Reversal via colonization, of social cognition and novel preference but not social avoidance.	Brain	(Desbonnet et al., 2014)
	Transcription BDNF IV isoform	↑ Neuronal IEG's & *Bdnf IV*, ↓ neurotransmission-related genes. Not reversed by colonization after weaning.	Amygdala	(Stilling et al., 2015)
	Brain Volume Dendritic morphology Spine density	↑ Certain regions but no significant difference in total volume. Aspinal interneuron and pyramidal neuron atrophy. short, thin, mushroom shape dendrites. Shorter, less branching in pyramidal neurons.	Hippocampus (DG), Amygdala (LA, BLA, CeA)	(Luczynski et al., 2016b)
	Social Preference/ Cognition	3 Chamber: ↓sociability and social novel preference. High variability between individuals.	Brain	(Stilling et al., 2018)

APP/PS1 & ♂ and ♀	Aβ	↓in Aβ deposition, ↓in neuroinflammation, ↑Aβ degradation enzymes. Reversal via colonization was most effective from other transgenic Aβ mice.	Brain	(Harach et al., 2017)
SJL/J	EAE	GF cannot develop EAE, microbiota required. This was reversed via microbial colonization.	CNS and immune tissue	(Berer et al., 2011)
BDF1-Thy1-αSynuclein, ♂	Parkinson's Disease/ αSynuclein	Unreactive microglia, less pathology. Colonization with human microbiota of individuals with PD also had more physical impairment than from healthy individuals. Reversed via colonization with microbiota and SCFA.	Caudoputamen Frontal cortex, Cerebellum, Substantia Nigra	(Sampson et al., 2016)
ASF ♂ and ♀	Microglia	↓ Immune response altered gene expression, immaturity. Reversed by microbiota colonization or SCFA administration. Tested: corpus callosum, cortex, hippocampus, olfactory bulb, and cerebellum.	Brain	(Erny et al., 2015)
CD11	Scrapie	Resistance to IC injection. ↑Survival rate, ↓ incidence of symptoms.	Brain, whole body	(Lev et al., 1971)
	Scrapie	Susceptible to IC injection. ↑ Survival rate, ↓ incidence of symptoms.	Brain, Whole body	(Lev et al., 1971)
GF Mouse	Stroke	Restraint stress: ↑lesion size, ↓amount of microglia/macrophages. Reversed via microbiota colonization.	Brain	(Singh et al., 2018b)
BACHD-FVB/N background ♂ and ♀	Myelination and oligodendroglia in Huntington's disease	↑Axon myelin thickness in BACHD-GF mice compared to BACHD-SPF in CC. ↑Proportion of small diameter axons in BACHD-GF ↓Myelin-related proteins and mature oligodendrocytes in all GF mice. ↓Mature oligodendrocytes in all GF mice.	Corpus callosum	(Radulescu et al., 2019)
Rat				
Wistar ♂	Peripheral Neurons	More irregular splitting in myelin in B6 deficient GF mice relative to conventional.	PNS	(Sumi et al., 1977)
Sprague Dawley	Serotonergic System	↑ Tryptophan brain uptake index.	BBB	(Jeppsson et al., 1979)
F344 ♂	Anxiety Transcription	OFT: ↑anxiety-like behavior, lower DA turnover rate. ↓sniffing in first two minutes of meeting, other behaviors (grooming, following, crawling) were normal.	Hippocampus Hypothalamus (PVN)	(Crumeyrolle-Arias et al., 2014)

Zebrafish				
Danio rerio	Anxiety Locomotion	OFT: ↑time that larva was mobile, no change in speed, ↑anxiety-like behavior, less thigmotactic behavior. This was reversed via colonization.	Brain, Whole larva	(Davis et al., 2016)
Japanese Quail				
	Emotional & novelty Reactivity Social separation	Novel Object Test: more time spent in near-object zone. Social separation test: ↓reactivity.	Brain	(Kraimi et al., 2018)

Table 3: Antibiotic studies of the microbiota-gut-brain axis, categorized by model organism.

Species	Antibiotic Cocktail	Time/ Behavior Assessed	Effects of antibiotic treatment	Ref.
Mouse				
NIH Swiss	-Ampicillin -Vancomycin -Neomycin -Metronidazole -Amphotericin-B	-NOR -Light/dark box -Social transmission of food preference -Corticosterone response to restraint stress Tested between 7-11 weeks	Altered gut microbiota composition in adulthood. ↓Anxiety-related behavior. Cognitive deficits in novel object discrimination and communication of cued food information. Alteration in the tryptophan/kynurenine metabolic pathway. Significant ↓in hippocampal BDNF, oxytocin, vasopressin expression.	(Desbonnet et al., 2015)
C57BL/6	-Bacitracin -Neomycin -Ampicillin -Meropenem -Vancomycin	-OFT -EPM -Tail suspension test (TST) -NOR -Barnes maze Tested between 8-11 weeks	Altered gut microbiota composition. ↓Novel object (but not spatial) discrimination. Brain-region specific changes in expression of relevant signaling molecules (i.e. BDNF, NMDA2B, Serotonin transporter, NPY).	(Frohlich et al., 2016)
	-Ampicillin & Sulbactam -Vancomycin -Ciprofloxacin -Imipenem & Cilastatin -Metronidazole	-NOR -Exercise Tested between 13-15 weeks	↓Novel object discrimination. ↓Hippocampal adult neurogenesis. Exercise was shown to ↑ neurogenesis. These effects are partially mediated by $Ly6C^{hi}$ Monocytes.	(Mohle et al., 2016)
	-Ampicillin -Streptomycin -Clindamycin	-TST, FST, Rotarod -Muscle strength test -NOR, -Y-maze -Hotplate test -3-Chamber -SIT Tested between 9-10 weeks	Depressive-like behavior observed in the FST and TST. ↓ Ability to discriminate social novelty. ↓ Hippocampal BDNF protein levels. ↑ Hippocampal TrkB protein levels. Altered spiking in hippocampal CA3. ↑Activated microglia/astrocytes in the hippocampus.	(Guida et al., 2018)

	-Neomycin -Bacitracin -Pimaracin	-OFT -3-Chamber SIT Tested between 4-7 weeks	Altered gut microbiota composition. ↓Locomotor activity in OFT. No difference in social behaviors between groups. Cross-fostering abolishes the behavioral differences at wk. 4.	(Tochitani et al., 2016)
BALB/c SPF & GF	Non-absorbable antibiotics: -Neomycin -Bacitracin -Pimaracin	-Light/dark test -Step down test Tested between 8-10 weeks	Altered gut microbiota composition. Anxiolytic-like effect in light/dark box and step-down inhibitory avoidance. ↑ Hippocampal BDNF expression.	(Bercik et al., 2011a)
BALB/c	-Penicillin V	-Locomotor activity - EPM -3-Chamber SIT Tested at 6 weeks	Altered gut microbiota composition. Anxiolytic-like effect observed in the EPM. ↑Aggression and ↓social avoidance behavior. ↑Avpr1b and cytokine expression in the frontal cortex. ↑Tight junction protein levels in the frontal cortex and hippocampus.	(Leclercq et al., 2017)
APPSWE/ PS1ΔE9	-Gentamicin -Vancomycin -Metronidazole -Neomycin -Ampicilli -Kanamycin -Colistin -Cefaperazone	Mice were culled for immunohistochemistry at 5- 6 months	Altered gut microbiota composition. Altered inflammatory cytokine composition. ↓Aβ plaque deposition. ↑Concentration in soluble Aβ levels. ↓Reactive gliosis surrounding Aβ plaques.	(Minter et al., 2016)
Thy1-α-synuclein	-Ampicillin -Vancomycin -Neomycin -Gentamycin -Erythromycin	-Beam Traversal, -Pole descent, -Adhesive removal -Hind Limb Clasping reflex sore, -Inverted Grid Tested at 12-13 weeks	Antibiotic administration ameliorated locomotor deficits induced by α-synuclein overexpression. ↓Microglial diameter in the caudate-putamen and substantia nigra.	(Sampson et al., 2016)
Rat				

Sprague Dawley	-Ampicillin -Vancomycin -Ciprofloxacin -Imipenem -Metronida-zole	- None	Altered expression of miRNAs in the amygdala and PFC. Amygdala: ↓ miR-206-3p & miR-219a-2-3p, ↑ miR-369-3p. PFC: ↓ miR219a-5p.	(Hoban et al., 2017)
	-Ampicillin -Vancomycin -Ciprofloxacin HCL -Imipenem -Metronida-zole	- OFT, EPM, FST - MWM, CRD -Hotplate Tested at 17-22 weeks	↓ Spatial memory observed in the MWM. ↑ Visceral sensitivity observed in CRD. Depressive-like behavior observed in the FST. Alterations in CNS serotonergic turn-over. ↓ Hippocampal CRHR1 expression, ↑in amygdala BDNF expression.	(Hoban et al., 2016a)
	-Vancomycin in three con-centrations Also assessed an antibiotic cocktail: -Pimaricin, bacitracin, neomycin	- NOR - OFT - MWM - CRD Tested at 8-11 weeks	Neonatal vancomycin significantly al-tered gut microbiota composition. ↑ Visceral sensitivity observed in CRD. Behavior in adulthood was not affected by early-life antibiotic administration. Early-life antibiotic cocktail also had no effect on behavior.	(O'Mahony et al., 2014)
	-Ampicillin -Vancomycin -Ciprofloxacin -Imipenem -Metronida-zole	- Assessment of cardio-respiratory measures 4 weeks	Blunts the ventilatory response to hy-percapnia due to decreased respiratory frequency. Blunts respiratory frequency during the peak hypoxic ventilatory response. Respiratory timing variability unaltered. ↓Systolic blood pressure Cardiorespiratory responsiveness to vagal afferent nerve stimulation is unaf-fected. Altered brainstem monoamine and monoamine metabolite concentrations. ↑ Distal ileum permeability.	(O'Connor et al., 2019)
Wistar	Dams were fed either control diet, or diet with 1% SST	- OFT, SIT, EPM, PPI - Marble burying Tested at 6-7 weeks	↓ Social interactions. Anxiety-like behavior observed in the EPM. Altered sensorimotor gating.	(Degroote et al., 2016)
Non-rodent				
species				

Zebrafish *Danio rerio*	Ofloxacin Ciprofloxacin Enrofloxacin Doxycycline Chlortetracycline Oxytetracycline	Social cohesion Tested at 3 months	↓ Social cohesion behavior. ↑ Anxiety-like behavior observed as a ↓in shoaling. Alterations in the expression of genes associated with locomotion.	(Wang et al., 2016)
Fruit fly *Drosophila melanogaster*	Tetracycline Rifampicin Streptomycin	Multiple choice mating tests	♂ and ♀ mating preference was abolished.	(Sharon et al., 2013)

Table 4: Prebiotic studies of the microbiota-gut-brain axis, categorized by model organism.

Species/Sex	Prebiotic	Treatment (time)	Effect	Ref.
Human				
Healthy ♂	Inulin-propionate ester	Acute	↓ Striatal anticipatory reward responses to high-energy foods.	(Byrne et al., 2016)
Healthy	RPS, RMS and inulin	2 weeks	↑Total SCFA with RPS and inulin. ↑Butyrate and acetate only with RPS. No changes seen with RMS.	(Baxter et al., 2019)
Type 2 diabetes ♀	Resistant dextrin (Nutriose®06)	8 weeks	↑ Depression, anxiety and stress (DASS). ↓ Cortisol, KYN, KYN/TRP ratio. Altered peripheral immune markers.	(Farhangi et al., 2018)
IBS ♂ ♀	Short-chain FOS	4 weeks	↓ Anxiety scores.	(Azpiroz et al., 2017)
Autism ♂ ♀	B-GOS® mixture	6 weeks	Improvement in social behavior symptoms and sleep in ASD subjects with B-GOS®.	(Grimaldi et al., 2018)
Mouse				
C57BL/6 ♂	FOS, GOS or both FOS and GOS	3 weeks	↓ Anxiety- and depressive-like behavior, stress-responsiveness, hypothalamic Nr3C1 and hippocampal Crhr1 expression. ↑ Pro-social behavior, hippocampal, 5-HT in PFC, BDNF, GABAR-B1 and -B2 expression.	(Burokas et al., 2017)
	FOS and GOS	6 weeks	↓ Chronic stress-induced social avoidance, cognitive dysfunction, anhedonia, HPA-axis hyper responsiveness anxiety- and depressive-like behavior.	(Burokas et al., 2017)
	3'Sialyllactose and 6'Sialyllactose	3 weeks	↓ Stressor-induced anxiety-like behavior and ↑ stress-induced ↓DCX+ immature neurons.	(Tarr et al., 2015)
	2´-fucosyllactose	12 weeks	↑ LTP, spatial learning, working memory and operant conditioning.	(Vazquez et al., 2015)
	Resistant starch	8 weeks	↓ Neuronal signaling in the ventromedial hypothalamus and PVN.	(So et al., 2007)
	β- glucan	8 weeks	↓ Neuronal signaling in the arcuate nucleus, ventromedial hypothalamus, PVN, periventricular nucleus and the NTS.	(Arora et al., 2012)
Diet-induced obese	Oligofructose-enriched inulin	9 weeks	↑ Neuronal signaling in the arcuate nucleus.	(Anastasovska et al., 2012)
CD1	B-GOS®	3 weeks	↓ LPS-induced anxiety-like behavior and HT2AR expression in the frontal cortex.	(Savignac et al., 2016)
BALB/cJ	FOS	7 weeks	↓ Aβ deposition and BAC levels. ↑ Hippocampal-dependent learning.	(Yen et al., 2017)

SOD1G^{93A} ♂♀	GOS	74 days	↓ Motor neuron death and spinal cord inflammatory markers.	(Song et al., 2013)
Rat				
Sprague Dawley ♂	2´-fucosyl-lactose	From PND3 and weaning	↑ LTP	(Oliveros et al., 2016)
	2´-fucosyl-lactose	5 weeks	↑ Operant Conditioning and LTP, PSD-95 protein levels in hippocampus and frontal cortex, as well as CaMKII and BDNF in the hippocampus.	(Vazquez et al., 2015)
	2´-fucosyl-lactose	5 weeks	↑ Operant Conditioning and long-term potentiation.	(Vazquez et al., 2016)
	Resistant Starch	65 Days	↑ Hypothalamic POMC expression.	(Shen et al., 2009)
	FOS or GOS	5 weeks	↑ Hippocampal BDNF and NR1 subunit expression. ↑ Hippocampal NR2A subunit and frontal cortex NR1 expression and d-serine levels by GOS.	(Savignac et al., 2013)
	B-GOS®	3 weeks	↑ Cortical GluN2A subunit.	(Kao et al., 2018)
	B-GOS®	3 weeks	↑ Cortical neuronal responses to NMDA and improved attentional set-shifting performance.	(Gronier et al., 2018)
	Chitosan oligosaccharides	10 Days	↑ Hippocampal-dependent memory. ↓ Hippocampal neuronal apoptosis, 8-OHdG, TNF-α and IL-1β levels.	(Jia et al., 2016)
♂♀	B-GOS®	3 weeks	↑ Hippocampal NR2A, SYN and BDNF levels PND22 and PND56	(Williams et al., 2016b)
Lister Hooded ♂	2´-fucosyl-lactose	From PND3 and weaning	↑ Cognition	(Oliveros et al., 2016)
Fischer 344 ♂	GOS, PLWC	9 weeks	↑ REM sleep rebound following stress exposure.	(Thompson et al., 2016)
	GOS, polydextrose, lactoferrin.	4 weeks	↓ Stress-induced learned helplessness and cFOS expression in the DRN. ↑ Basal BDNF in prefrontal cortex by GOS, polydextrose and lactoferrin.	(Mika et al., 2017)
	GOS, PLWC	40 Days	↑ Dendritic spine density of rat hippocampal neurons.	(Waworuntu et al., 2016)
Pig				
♂	Sialyllactose	3 weeks	No effect on recognition Memory or diurnal Activity.	(Fleming et al., 2018)
	Lactoferrin	5 weeks	↑ Hippocampal BDNF and cognitive function.	(Chen et al., 2015)
	GOS, PLWC	2 weeks	↑ Spatial learning. ↓ Cortical grey/white matter.	(Mudd et al., 2016)
	GOS and polydextrose	3 weeks	↑ Exploratory behavior and recognition memory, ↓ Hippocampal 5-HT.	(Fleming et al., 2017)

Table 5: Probiotic studies of the microbiota-gut-brain axis, categorized by model organism.

Species Parameter	Probiotic	Treatment (Time)	Effect	Ref.
Human				
Healthy ♂	*B. longum* 1714	4 weeks	↑ Neurocognitive performance (paired associative learning). ↑ Fz mobility. ↓ Cz theta power after end of probiotic administration.	(Allen et al., 2016)
	L. rhamnosus (JB-1) ™	4 weeks	Does not significantly impact HPA axis, stress, and cognition.	(Kelly et al., 2017)
♀	FMP: *B. animalis* subsp. *lactis* Classic yogurt starters: *S. thermophiles*, *L. bulgaricus,* *L. lactis* subsp *lactis*	4 weeks	↓ Reactivity in widely distributed network during emotional attention task. ↓ BOLD signal in amygdala, mid insula cortex, primary somatosensory cortex in emotional attention task. Altered PAG resting state network.	(Tillisch et al., 2013)
♂ ♀	Ecologic®825: *L. casei, L. paracasei,* *B. lactis, L. salivarius, B. lactis, L. plantarum* *B. bifidum, L. acidophilus, L. lactis*	4 weeks	Change in gut microbiota profile. ↓ Some anxiety and depressive measures.	(Bagga et al., 2018b)
	Ecologic®825: see above for composition	4 weeks	Changes in functional connectivity but no changes in structural connectivity.	(Bagga et al., 2018a)
	Ecologic®Barrier: *B. bifidum, B. lactis, L. acidophilus,* *L. brevis, L. casei, L. salivarius, L. lactis*	4 weeks	↓ Aggression and rumination in response to depressive thoughts (LEIDS-r test).	(Steenbergen et al., 2015)
	L. casei Shirota (Yakult)	3 weeks	Only improvement in depression in POMS scale for people at the lowest end of the mood scale.	(Benton et al., 2007)

	Group 1: Probiotic yogurt *L. acidophilus* LA5, *B. lactis* BB12 Group 2: Capsule *L. casei*, *L. acidophilus* , *L. rhamnosus* , *L. bulgaricus, B. breve, B. longum, S. thermophilus,* FOS	6 weeks	Improvement in GHQ scale with either probiotic treatment.	(Mohammadi et al., 2016)
	L. helveticus R0052 and *B. longum* R0175	30 days	↓ Anxiety via HADS score.	(Messaoudi et al., 2011a)
	B. subtilis: containing 75% in spore form and 25% in vegetative form	4 weeks	Only impacted microbiota composition. No effect on GI symptoms or general wellness.	(Hanifi et al., 2015)
Aging (<60) ♂ ♀	L. reuteri	12 weeks	No persisting effects on depression, anxiety or perceived stress.	(Ostlund-Lagerstrom et al., 2016)
Aging (60-75) ♂ ♀	*L. helveticus* IDCC3801	12 weeks	↑ Cognitive performance in RVIP and Stroop Color-Word task (cognitively demanding tasks).	(Chung et al., 2014)
Alzheimer's Disease ♂ ♀	Capsule: *L. acidophilus, L. casei, B. bifidum, L. fermentum*	12 weeks	↑ MMSE score. Change in blood lipid profile and carbohydrate metabolism factors.	(Akbari et al., 2016)
Chronic fatigue ♂♀ syndrome	L. casei strain Shirota	8 weeks	↓ Anxiety symptoms.	(Rao et al., 2009)
Urinary-free cortisol 10-50ng/ml (low) ♂ ♀	*L. helveticus* R0052 and *B. longum* R0175	30 days	↑Perceived stress score, hospital anxiety, depression scale score. ↑HSCL-90 subscores for obsessive-compulsive, anxiety, and depression. ↑↑ HSCL-90 in Factor 1 (anxiety and depression).	(Messaoudi et al., 2011b)
HIV-1^{+} ♂	Vivomixx®: L. plantarum, *S.* thermophiles, B. breve, L. paracasei, L.delbrueckii subsp. Bulgaricus, L. acidophilus, B. longum, B. infantis	6 months	↑ Neurocognitive performance.	(Ceccarelli et al., 2017a)
♂ ♀	Vivomix®: (See composition above)	6 months	↑ Verbal and visual memory.	(Ceccarelli et al., 2017b)

IBS ♂ ♀	*B. longum* NCC3001	6 weeks	↓ HAD-A and D scores indicating ↓ in anxiety/ depression. ↑ Quality of life.	(Pinto-Sanchez et al., 2017b)
	L. paracasei, ssp. paracasei F19 *L. acidophilus* La5 *B. lactis* Bb12	8 weeks	No significant psychological changes.	(Simren et al., 2010)
MDD ♂ ♀	Capsule: *L. acidophilus, L. casei, and B. bifidum*	8 weeks	↓ BDI score.	(Akkasheh et al., 2016)
	L. helveticus R0052 and *B. longum* R0175 (CNCM strain I-3470)	8 weeks	↓ BDI score (depressive index). ↓ Kynurenine: Tryptophan ratio.	(Kazemi et al., 2019)
	L. Plantarum 299v	8 weeks	↑ APT and CVLT total recall of trials 1–5 ↓ Kynurenine concentration ↑ 3-hydroxykynurenine: kynurenine ratio	(Rudzki et al., 2019)
MS ♂ ♀	Capsule: *L. acidophilus, L. casei, B. bifidum* *L. fermentum*	12 weeks	↑BDI, EDSS, DHQ scores (depression, diet and multiple sclerosis scores).	(Kouchaki et al., 2017)
Normal weight obese syndrome and obesity ♀	1 "bag": *S. thermophiles, B. animalis* subsp. *Lactis*, *S. thermophilus, B. bifidum* *L. delbrueckii* spp. *Bulgaricus , L. lactis* subsp. *Lactis, L. acidophilus, L. plantarum , L. reuteri*	3 weeks	↓ positivity to BUT. ↓ EDI-2 responses.	(De Lorenzo et al., 2017)
Obesity ♂ ♀	*L. rhamnosus* CGMCC1.3724	24 weeks	↑ Body esteem in ♀s, ↓ Depression score in ♀s.	(Sanchez et al., 2017)
Pregnancy	*L. rhamnosus* HN001	<6 months	↓ Postpartum depression and anxiety scores.	(Slykerman et al., 2017)
Schizophrenia ♂ ♀	Bifiform Balance: *L. rhamnosus* strain GG *B. animalis* subsp. lactis Bb12	14 weeks	↓ *C. albicans* antibodies in ♂ serum, associated with ↓ psychiatric symptom occurrence.	(Severance et al., 2017)
	L. rhamnosus strain GG *B. animalis* subsp. *lactis* strain Bb12	14 weeks	No changes in frequency of psychotic symptoms. ↓ Incidence of severe bowel difficulties. ↓ Acute von Willebrand factor, ↑ MCP-1, BDNF, RANTES, MIP-1.	(Tomasik et al., 2015)
	Bifiform Balance: *L. rhamnosus* strain GG *B. animalis* subsp. lactis Bb12	2 weeks	No differences in PANSS total symptom score. ↓ Incidence of severe bowel difficulties.	(Dickerson et al., 2014)

Pregnancy	*L. rhamnosus GG, L. rhamnosus LC705, B. breve Bb99, and Propionibacterium freudenreichii- subspecies shermanii*	From 36 weeks' gestation until the birth of the infant	Analyzed 81 randomly selected colostrum samples from a bank of 500. ↑ Human milk oligosaccharides: 3-fucosyllactose and 3'-sialyllactose in colostrum ↓ Human milk oligosaccharides: difucosyllacto-N-hexaose, lacto-N-tetraose, lacto-N-fucopentaose I, and 6'-sialyllactose.	(Seppo et al., 2019)
Stress ♂ ♀	Probio-Stick: *L. acidophilus* Rosell-52 *B. longum* Rosell-175	3 weeks	↓ Stress-induced abdominal pain and nausea/vomiting. ↓ Flatulence, gas production. No effect on other symptoms (physical, psychological, sleep).	(Diop et al., 2008)
Stress/ Exhaustion ♂ ♀	Multiobionta: Probiotic culture blend *L. acidophilus, B. bifidum, B. longum*	6 months	↑ in fatigue and stress.	(Gruenwald et al., 2002)
Moderate stress ♂ ♀	*L. plantarum* DR7	4, 8 and 12 weeks	↓ Stress and anxiety using DASS-42, but not PSS-10, questionnaires. No effect on depression. ↑ Anti-inflammatory cytokines and ↓pro-inflammatory cytokines in young adults. ↓ Pro-inflammatory cytokines in normal adults over 12 weeks. ↑ Verbal learning and memory in young adults ↑ Basic attention, social emotional cognition and associate learning in normal adults over 12 weeks. ↓ IDO/TDO, kynurenine, cortisol, IFN-γ and TNF-α. ↑ TPH, Serotonin, IL-4, IL-10.	(Chong et al., 2019)
Student exam stress ♂ ♀	*L. casei* strain Shirota YIT 9029	8 weeks	↓ Physical symptoms of stress/anxiety	(Takada et al., 2016)
	B. bifidum R0071 or *L. helveticus* or *B. infantis*	6 weeks	↑ Healthy days (i.e. no flu/cold) only from *B. bifidum.* ↓ Reports of symptoms lasting more than a day in participants receiving *B. bifidum.* Proportion of participants reporting cold/flu between weeks 2 and 3 lower in those receiving *B. bifidum* or *B. infantis.*	(Langkamp-Henken et al., 2015)
	L. plantarum 299v	14 days	No difference in perceived stress. ↑ *L. plantarum* 299v and *Lactobaccili* on Day 14 in saliva.	(Andersson et al., 2016)

	L. casei strain Shirota (YIT 9029) Formulated in 100mL of milk	8 weeks	No change in psychological parameters (anxiety, depression scales). ↓ Physical symptoms i.e. runny nose, cold.	(Kato-Kataoka et al., 2016)
TBI ♂	240 ml of fermented milk with the *L. johnsonii* Given along with 30g glutamine	6-14 days via enteral tube	↓ Infection rate, length of stay in ICU, days on mechanical ventilator.	(Falcao de Arruda and de Aguilar-Nascimento, 2004)
Type 2 Diabetes	Capsule: *L. acidophilus, L. casei, B. bifidum* *L. fermentum,* vitamin D3	12 weeks	Improved BDI, BAI, GHQ scores (↓anxiety and depression).	(Raygan et al., 2018)
Low mood ♂♀	*L. helveticus, B. longum*	8 weeks	No effect.	(Romijn et al., 2017)
Mouse				
Stress ♀	*Pediococcus acidilactici*	36 days	No effect on tonic immobility induced by fear. No effect in OFT, ↑ Memory (not due to emotional reactivity).	(Parois et al., 2017)
AKR – DSS ♂	*B. longum* NCC3001	2 to 3 weeks	↓ Anxiety-like behavior in DSS.	(Bercik et al., 2011b)
	B. longum NCC3001		↓ AH neuron excitability, resistance and magnitude of cationic current.	(Khoshdel et al., 2013)
Balb/c ♂	*B. longum 1714* or *B. breve 1205*	6 weeks	↓ Bodyweight gain from *B. longum.* ↓ Body temperature ↑during stress-induced hyperthermia. ↓ Anxiety in marble burying with either strain. ↓ Anxiety via EPM in *B. breve* but no difference in locomotion. ↓ Latency in OFT in *B. longum* group. ↓ Immobility time in FST for *B. longum* group. ↑ Spleen weight in *B. breve.*	(Savignac et al., 2014)
	L. rhamnosus	29 days	↓ Stress-induced hypothermia, anxiety (EPM). ↓ $GABA_{B1b}$ mRNA in basolateral and central amygdala, locus coeruleus, DG, CA3, CA1. ↓ *GABAAα2* mRNA in CG1, PrL and IL cortical areas, and BLA, CeA. ↑ *GABAAα2* mRNA in the DG. Effects abolished through vagotomy.	(Bravo et al., 2011)

Alzheimer's Disease ♂	SLAB51: *S. thermophiles, B. longum, B. breve, B. infantis, L. acidophilus, L. plantarum, L. paracasei, L. delbrueckii subsp. bulgaricus, L. brevis*	4 months	↓ Oxidative stress in brain. ↓ Cognitive decline, brain damage, Aβ peptide accumulation.	(Bonfili et al., 2018)
ICR: Vascular ♂ dementia model	*C. butyricum*	6 weeks	↑ Spatial memory, ↓ Neuronal apoptosis, ↑ Butyrate in brain.	(Liu et al., 2015)
ICR: ♂ Ischemia Injury	*C. butyricum*	2 weeks	↓ Neurological deficit score,↓ Hippocampal neuron karyopyknosis. ↓ Apoptosis in CA1 via TUNEL.	(Sun et al., 2016a)
Shank3 KO (Jackson Labs) ♂ ♀	*L. reuteri*	3 weeks	GABAR expression correlated with *L. reuteri* in mice. Probiotic modifies social (in ♂s) and repetitive behavior (♂s and ♀s), ↑GABAR (regional and sex-dependent magnitudes) and oxytocin expression.	(Tabouy et al., 2018)
Swiss Albino SD & CUMS ♂	*L. plantarum* MTCC 9510	28 days	↓ SD-induced anxiety and depression (FST, EPM). ↑ Learning and memory (MWM), ↓ BBB permeability. Abolished *Bdnf* decrease in hippocampus. Prevented some stress-induced microbiota alterations	(Dhaliwal et al., 2018)
Shank3 KO (Jackson Labs) VPA Mouse Model of ASD BTBR ♂	*L. reuteri*	4 weeks	In all three strains, rescued impaired sociability as measured by three-chamber sociability, reciprocal social interaction and/or social novelty tests.	(Sgritta et al., 2019)
C57Bl/6J				
Maternal Separation ♂	*B. CECT* 7765	21 days	Partially attenuated exaggerated HPA stress response. ↓ Vulnerability to stress in adulthood. ↓ Anxiety, catecholaminergic hyperactivity in adulthood. Protected against stress-induced microbiota alterations.	(Moya-Perez et al., 2017b)
TBI ♂	*C. butyricum*	14 days before and after TBI	Ameliorated neurological deficits and brain edema size. ↓ Degenerating neurons, ↑ Occludin and ZO-1 expression at BBB to ameliorate ↑permeability from TBI. ↑ P-Akt/Akt, Bcl-2 along with ↓ Bax indicating less neuronal. apoptosis, ↑ GLP1 in colon, GLP1-R in brain.	(Li et al., 2018a)

C. rodentium infection ♀	Lacidofil: *L rhamnosus* and *L helveticus*	10 days	Attenuates WAS non-spatial memory deficit. Ameliorates *BDNF* and *c-Fos* in hippocampus after WAS.	(Gareau et al., 2011)
TNBS-induced colitis and memory impairment ♂	*L. plantarum*	colitis: 3 days memory: 5 days	Reversed memory impairments (spontaneous alteration in Y-Maze). Restored some microbiota perturbations. ↑ *Bdnf* and↓ NF_KB activation in hippocampus and LPS in blood.	(Lee et al., 2018a)
Chronic social defeat stress ♂	*L. rhamnosus* (JB-1) ™	28 days	↓ Stress-induced anxiety. Prevented deficits in social interaction with conspecifics.	(Bharwani et al., 2017)
Maternal HFD ♂	*L. reuteri*	4 weeks	Rescues impairments in LTP in DAergic VTA neurons.	(Buffington et al., 2016)
Subchronic social defeat stress ♂	*L. helveticus* MCC1848	24 days	restored normal sucrose consumption in the sucrose preference test ↓ Anxiety-like behavior in the SIT. No effect on polydipsia-like behavior. Rescued Drd3, Htr1a sCSDS-induced deficit in NAc.	(Maehata et al., 2019)
DSS- colitis ♂ ♀	*L. rhamnosus* and *L. helveticus*	20 days	Rescued some decreases in NOR, anxiety and c-fos in CA1.	(Emge et al., 2016)
Chronic stress ♂	*L. helveticus* R0052 or /and *B. longum* R0175	14 days	Combination of both probiotics reversed distension pain hypersensitivity at larger volumes. Prevented GR decrease in hypothalamus and hippocampus if pretreated with both probiotics or *B. longum.* Only both probiotics prevented this ↑in the PFC.	(Ait-Belgnaoui et al., 2018)
Maternal separation – early life stress ♂	*L. plantarum* PS128	28 days	Restores sucrose preference (↓in ELS/no probiotic). ↑ Locomotor activity, ↓ anxiety in EPM in naïve mice. ↑ DA and DAergic metabolites in PFC in early life stress. ↓ HVA: DA ratio. No change in DAergic activity in striatum.	(Liu et al., 2016b)
6JNarl: GF ♂	*L. plantarum* PS128	16 days	↓ Anxiety-like behavior, ↑ Locomotor activity.	(Liu et al., 2016a)
6N: MIA	*B. fragilis*	6 days	Corrected microbiota changes in MIA offspring. Prevented/↓MIA-induced anxiety (OFT, marble burying), ↓deficits in sensorimotor gating. Did not improve social deficits.	(Hsiao et al., 2013)

WAS ♂	*L. helveticus* R0052 and *B. longum* R0175	2 weeks	↓ cFos⁺ neurons responding to WAS in PVN, CA3, and amygdaloid nucleus (↑in non-WAS/probiotic compared to other control animals). ↑ *Bdnf* in hypothalamus in response to WAS. ↓ Expression of cytoskeleton organization, microglia activation, synaptogenesis and cell adhesion markers in hypothalamus in response to WAS.	(Ait-Belgnaoui et al., 2014)
Mouse & Rat				
Swiss-Webster *Ex-vivo* recordings	*L. reuteri* DSM 17938	9 days	↓ Spontaneous mesenteric nerve firing activity. Effect not inhibited by smooth muscle relaxation or vagotomy. Partial evoked antagonism of TRPV1. ↓ Distension evoked firing via TRPV1 antagonism. Supernatants also able to exhibit antagonism. ↓ Calcium rise and ionic current in dorsal root ganglia primary culture.	(Perez-Burgos et al., 2015)
Rat				
Sprague-Dawley ♂	*Faecalibacterium prausnitzii* (ATCC 27766)		Prevented and treated depressive-like or anxiolytic-like behaviors caused by CUMS. Rectified CUMS-induced weight loss. ↑ Cecal acetate, propionate and n-butyrate levels. ↓ CUMS-induced circulating corticosterone and CRP increase. ↑ IL-10 level, and ↓IL-6 induced by CUMS.	(Hao et al., 2019)
Swiss-Webster *Ex-vivo* electrophysiology ♂	*L. rhamnosus* (JB-1) ™ *L. salivarius*	N/A	↑Firing rate of mesenteric afferent bundles. 70% of single unit afferent nerves also had an ↑ firing rate. Administration does not reduce firing rate after distension. Effects abolished by vagotomy.	(Perez-Burgos et al., 2013)
Brown Norway Water avoidance stress (WAS) ♂	Lacidofil Powder: 95% *L. rhamnosus* R0011 5% *L. helveticus* R0052	7 days	Prevents stress induced bacterial adherence to enterocytes. Prevents bacterial translocation to mesenteric lymph nodes after WAS. No apparent effect on intestinal histology. Inhibit chronic stress elevation of ion secretion in intestines. No impact on permeability in ileum or colon.	(Zareie et al., 2006)

FSL and FRL: HFD ♂	Ecologic Barrier: *B. bifidum*, *B. lactis*, *L. acidophilus*, *L. brevis*, *L. casei*, *L. salivarius*, *L. lactis*	12 weeks	Protected against depressant effects of HFD in FSL (FST). No effect on locomotor activity.	(Abildgaard et al., 2017a)
Aging	Probiotic Mixture KF (1:1 ratio): *L. curvatus* HY7601 *L. plantarum* KY1032		Reversed age-dependent ↓in spontaneous alteration (Y Maze). No significant effect on escape latency (MWM). ↑Hippocampal DCX, BDNF and phosphorylated CREB relative to control aged mice, ↓activation of mTOR pathway.	(Jeong et al., 2015)
Maternal separation ♂	*B. breve* 6330	42 days	↑ BDNF IV mRNA in control rats given probiotic (not affected by maternal separation).	(O'Sullivan et al., 2011)
Depression – maternal separation ♂	*B. infantis 35624*	45 days	Normalized effects of maternal separation in FST. ↓ 5-HIAA in amygdaloid cortex.	(Desbonnet et al., 2010)
Chronic restraint stress model ♂	*L. helveticus* NS8	~27 days	↓ Anxiety-like and depressive-like behavior. ↑ Recognition memory. ↑ Hippocampal *bdnf*, NE, 5-HT.	(Liang et al., 2015a)
Maternal separation stress	Lacidofil Powder: 95% *L. rhamnosus* R0011 5% *L. helveticus* R0052	P4-P20 (17 days)	Transient *L.* colonization. Restored ion transport and permeability after WAS in adult life (persisting effect). Abolished MS-induced HPA overactivation.	(Gareau et al., 2007)
♂	Lacidofil Powder: 95% *L. rhamnosus* R0011 5% *L. helveticus* R0052	Administered to dams from P2-P14 (13 days)	Restored age-appropriate forgetting (infantile amnesia) and relapse-resistant extinction of aversive memories during infancy (P17). No effect on anxiety or locomotor activity in pups or dams. No effect on maternal care behavior (pup retrieval).	(Cowan et al., 2016)
♂	Lacidofil Powder: 95% L. rhamnosus R0011 5% L. helveticus R0052	To dams from P2-P14 (13 days)	Restored age-appropriate neural activity in the pre-frontal cortex following fear expression and inhibition during infancy (P17).	(Cowan et al., 2019)
♂ ♀	Lacidofil Powder: 95% *L. rhamnosus* R0011 5% *L. helveticus* R0052	Administered to dams from P2-P14 (13 days)	Restored normative timing of physical puberty onset in both sexes (reversed stress-induced delay in preputial separation for males, stress-induced acceleration of vaginal opening in females).	(Cowan and Richardson, 2018)

♂♀	*L. rhamnosus* GG	~4 weeks	Ameliorate ↓ in exploration and ↑ in anxiety from stress. Altered gene expression in hippocampus (no behavior in ♀s).	(McVey Neufeld et al., 2017)
♂	*B. infantis*	14 days	No effect in FST. ↓ 5-HIAA in frontal cortex. ↓ DOPAC in amygdaloid cortex. No effect on CRF mRNA in hypothalamus.	(Desbonnet et al., 2008)
	Ecologic Barrier: *B. bifidum*, *B. lactis*, *L. acidophilus*, *L. brevis*, *L. casei*, *L. salivarius*, *Lactococcus lactis*	11 weeks	↓ Depression (FST). No locomotor effect (OFT). ↓ Expression of HPA axis genes in hippocampus. ↑ Expression of neuroprotective genes (*Trek2*, *Traak*).	(Abildgaard et al., 2017b)
	L. reuteri	9	↓ Firing threshold of afterhyperpolarization myenteric neuron. ↓ Slow after-hyperpolarization potential of sensory neurons. ↓ Potassium-dependent calcium channel opening.	(Kunze et al., 2009)
	L. rhamnosus and *B. longum*	12 days	↓ Depression-like behavior. ↑ Expression of GABA-A Receptor subunits in hippocampus.	(Liang et al., 2017)
	L. casei 54-2-33	14 days	↑ Anxiety (OFT). ↓ Expression of 5-HT_{1A} mRNA in hippocampus.	(Barrera-Bugueno et al., 2017)
Response to CRD after partial ♀ restraint stress	*L. farciminis*	14 days	Probiotic prevented ↑ in c-Fos expression in sacral spinal cord, PVN and MeA.	(Ait-Belgnaoui et al., 2009)
Antibiotic microbiota depletion ♂	*L. fermentum* NS9	41 days (behavior tested at day 31)	↓ Myeloperoxidase activity in colon. Alleviated ampicillin-induced anxiety (EPM). Alleviated memory deficits seen in MWM in ampicillin-treated animals. Prevented ampicillin-induced MR and NMDA-R decrease in hippocampus.	(Wang et al., 2015)
HA induced neuro-inflammation model ♂	*L. helveticus* NS8	2 weeks	↓ Anxiety-like behavior (EPM). ↑ Learning and memory (MWM). ↓ 5-HT in cerebellum and hippocampus but did not restore regional. ↑ 5-HIAA in HA brain.	(Luo et al., 2014)
Myocardial infarction ♂	*L. helveticus* *B. longum*	4 weeks	↓ Bax/Bcl-2 and Caspase-3 levels in DG, medial amygdala and lateral amygdala but not CA1 or CA3 ↓ apoptosis. Differences in phopsho-Akt:Akt ratios in these regions.	(Girard et al., 2009)

CRD ♂	*L. reuteri*	9 days	Inhibition of ↑ heart rate in response to CRD. ↓ Single unit discharge of PNS neurons in response to distention. No effect on pain via tail flick or paw pressure tests.	(Kamiya et al., 2006)
Colitis induced by zymosan ♂	*L. rhamnosus* GG	40 days	Measurements taken in adulthood after early-life colitis induction. ↓ Visceromotor response to distension. No change in DA or its metabolites in brainstem. ↑ DA and DOPAC in frontal cortex. ↑ NA and 5-HIAA in cerebellum. ↓ His in brainstem ↓ Glu and Lys in subcortex. ↓ Glu, Lys, His, Taurine in frontal cortex. ↓ GABA in frontal cortex, subcortex and cerebellum.	(Kannampalli et al., 2014)
Trans-generational paternal stress ♂	Lacidofil Powder: 95% *L. rhamnosus* R0011 5% *L. helveticus* R0052	Maternally P2-P14 (13 days)	Restored age-appropriate forgetting and relapse-resistant extinction of aversive memories in F1 offspring during infancy (P17).	(Callaghan et al., 2016)
Sprague-Dawley & WKY: CRD	*L. salivarius* UCC118, *B. infantis* 35624, or *B. breve* UCC2003	14 days	↑ Pressure threshold in Sprague-Dawley rats in response to distension if given *B. infantis* or *B. breve.* ↑ Pressure threshold in WKY rats given *B. infantis.* ↓ Pain behavior in both strains when given *B. infantis.*	(McKernan et al., 2010)
Wistar ♂	*L. helveticus, B. longum*	7 days	↓ Anxiety in marble burying.	(Messaoudi et al., 2011a)
	L. helveticus, B. longum	7 days	No rewarding properties of probiotic in conditioned place preference relative to morphine. No learning and memory deficit in passive avoidance paradigm.	(Messaoudi et al., 2011b)
	VSL #3	6 weeks	Effect on brain gene expression (>300 genes). Attenuate age-related decrease in LTP. ↓ Microglial activation in hippocampus.	(Distrutti et al., 2014)
HFD ♂	L. paracasei	12 weeks	↓ Microglial activation, ↓ Cognitive dysfunction.	(Chunchai et al., 2018)
AD	*L. plantarum*	60 days	↑ Performance in MWM in AD+Probiotic group.	(Nimgampalle and Kuna, 2017)

Diabetes ♂	Mix: *L. acidophilus, B. lactis, L. fermentum*	8 weeks	↑ Performance on MWM in diabetes probiotic. ↑ Synaptic transmission (electrophysiology).	(Davari et al., 2013)
Zebrafish				
♂ ♀	*L. rhamnosus*	4 weeks	↑ Exploration, attention. ↑ Brain *bdnf*, serotoninergic system genes.	(Borrelli et al., 2016)
Drosophila				
♂ ♀	*L. plantarum* L168	2-3 days	↑ Social behavior in kdm5-deficient flies. ↓ Intestinal permeability ↓ Number of intestines with defects in kdm5-deficient flies. ↓ 5-HT levels in kdm5-deficient flies. Restored intestinal barrier integrity. KDM5 demethylase affects social behavior through the gut-microbiome-brain axis. 3.5-fold increase in median survival of kdm5-deficient flies. Only GF flies with kdm5-deficiency were viable.	(Chen et al., 2019)

Table 6: Tools used in the analysis of the gut microbiome.

Tool	Function	Based on:	Platform	Advantages	Disadvantages
Biomarker Profiling	Microbiota Composition	DNA	NGS	- Somewhat Cost Effective - Semi-quantitative	Lacks Functional Information
Metagenomics	Microbiota Functional Gene Capacity	DNA	NGS	Can Achieve Strain-level Resolution	- Expensive - Computationally intensive
Metabolomics	Metabolic Productivity	Metabolites	LC/GC-MS	- Targeted or Untargeted - Semi-quantitative	Origin of Metabolite is Unclear
Metatranscriptomics	Microbial Functional Gene Expression	RNA	NGS	Host and Microbial Gene Transcripts	- Requires RNA Preservation - Host Genes may Dominate
Metaproteomics	Protein Expression	Protein	LC/GC-MS	Semi-quantitative	Protein Origin not Clear

XVIII. Tables Abbreviations

↓ - decrease/ reduction/ downregulation

↑ - increase/ enhancement/ upregulation

5-HIAA - 5-Hydroxyindoleacetic acid

5-HT – 5-hydroxytryptamine or serotonin

5-$HT_{1A/2A}$R - Serotonin 1A/2A receptor

8-OHdG - 8-Oxo-2'-deoxyguanosine

Aβ - Amyloid β

AH – Afterhyperpolarization

APT - Attention and perceptivity test

ASD – Autism spectrum disorder

ASF - Altered schaedler flora

B. acidophilus– Bifidobacterium acidophilus

B. adolescentis – Bifidobacterium adolescentis

B. animalis – Bifidobacterium animalis

B. bifidum – Bifidobacterium bifidum

B. breve – Bifidobacterium breve

B. catenulaturm– Bifidobacterium catenulaturm

B. dentium– Bifidobacterium dentium

B. fragilis – Bifidobacterium fragilis

B. infantis– Bifidobacterium infantis

B. lactis – Bifidobacterium lactis

B. longum – Bifidobacterium longum

B. subtilis – Bifidobacterium subtilis

B-GOS® - Bimuno-galactooligosaccharide

BACHD - Bacterial artificial chromosome model of HD

BAI - Beck anxiety inventory

BBB – Blood-brain barrier

BDF1 - Bromodomain-containing factor 1

BDI - Beck depression inventory

BDNF – Brain-derived neurotrophic factor

BLA – Basolateral amygdala

BOLD - Blood-oxygen-level dependent

BrdU – Bromodeoxyuridine

BUT - Body uneasiness test

C. rodentium – Citrobacter rodentium

C. butyricum - Clostridium butyricum

C. perfringens - Clostridium perfringens

C. difficile - Clostridium difficile

CA1/3 - Cornu Ammonis 1/3

CaMKII – Calcium calmodulin-dependent protein kinase

CC - Corpus callosum

CeA - Central nucleus of the amygdala

CNS – Central nervous system

Cog – Cognition

CRD – Colorectal distension

CREB - cAMP response element-binding protein

CRF - Corticotropin-releasing factor

CRHR1 - Corticotropin-releasing hormone receptor 1

CRP - C-reaction protein

CUMS - chronic unpredictable mild stress

CVLT - California verbal learning test

DA – Dopamine

DAergic – Dopaminergic

DASS - Depression anxiety stress scales

DCX – Doublecortin

DG – Dentate gyrus

DHQ - Diet history questionnaire

DNA - Deoxyribonucleic acid

DOPAC - Dihydroxyphenylacetic acid

Drd3 - Dopamine receptor D3

DREADD - Designer receptors exclusively activated by designer drugs

DRN - Dorsal raphe nucleus

DSS - Dextran sulphate sodium

EAE - Experimental autoimmune encephalomyelitis

EDI - Eating disorders inventory

EDSS - Expanded disability status scale

ELS - Early life stress

FOS – Fructooligosaccharide

EPM – Elevated plus maze

FMP - Fermented milk product

FMT - Fecal microbiota transplant

FRL - Flinders resistant line

FSL - Flinders sensitive line

FST - Forced-swim test

GABA - γ-Aminobutyric acid

Gcg – Glucagon

GF – Germ-free

GHQ - General health questionnaire

GI - Gastrointestinal

GOS – Galactooligosaccharide

HA - Hyperammonemia

HADS - Hospital anxiety and depression scale

HCL – Hydrochloric acid

HD - Huntington disease

HFD – High-fat diet

HIV - Human immunodeficiency virus

HPA - Hypothalamic-pituitary-adrenal

HSCL - Hopkins symptom checklist

Htr1a - Serotonin 1A receptor

Ht2ar – Serotonin 2A receptor

HVA - Homovanillic acid

Hyperammonemia (HA)

IBS - Irritable bowel syndrome

IC – Intracerebral

ICR - Institute of Cancer Research

IDO - Indoleamine 2,3-dioxygenase

IEG – Immediate early gene

IFNγ - Interferon gamma

IL (Immunology) – Interleukin

IL (Cortex) - Infralimbic cortex

KDM5 - Histone demethylase kdm5

KM - Chinese kun ming mouse

KYN - Kynurenine

L. acidophilus – Lactobacillus acidophilus

L. brevis– Lactobacillus brevis

L. bulgaricus – Lactobacillus bulgaricus

L. casei – Lactobacillus casei

L. curvatus – Lactobacillus curvatus

L. delbrueckii – Lactobacillus delbrueckii

L. farciminis– Lactobacillus farciminis

L. fermentum– Lactobacillus fermentum

L. helveticus – Lactobacillus helveticus

L. johnsonii– Lactobacillus johnsonii

L. paracasei – Lactobacillus paracasei

L. plantarum – Lactobacillus plantarum

L. reuteri – Lactobacillus reuteri

L. rhamnosus – Lactobacillus rhamnosus

L. salivarius– Lactobacillus salivarius

LA – Lateral amygdala

LC/GC-MS - Liquid chromatography/ gas-chromatography-mass spectrometry

LDB – Light/dark box

LD - Light/dark preference

LEIDS-r - Leiden index of depression sensitivity-revised

LPS – Lipopolysaccharides

LTP – Long-term potentiation

MB – Marble burying

MCP-1 - Monocyte chemoattractant protein-1

MDD - Major depressive disorder

MeA - Medial amygdala

MGBA – Microbiota-gut-brain axis

MMSE - Mini mental state exam

MIA – Maternal immune activation

MIP-1 - Macrophage inflammatory protein-1

MiR/ miRNA - microRNA

mRNA - Messenger ribonucleic acid

MS - Multiple Sclerosis

MR - Mineralocorticoid receptor

mTOR - Mammalian target of rapamycin

MWM – Morris water maze

NA – Noradrenaline

NAc – Nucleus accumbens

NE – Norepinephrine

NF_KB - Nuclear factor kappa-light-chain-enhancer of activated B cells

Ngfi-a - Nerve growth factor inducible A

NGS – Next-generation Sequencing

NIH - National Institutes of Health

NMRAR - N-methyl-D-aspartate receptor

NMRI - Naval medical research institute

NOR – Novel object recognition

NPY - Neuropeptide Y

NR1/2 – NMRAR 1/2

Nr3C1 - Nuclear Receptor Subfamily 3 Group C Member 1

NSF - Novelty suppressed feeding

NTS - Nucleus tractus solitaris (the nucleus of the solitary tract)

OFT - Open-field test

PAG - Periaqueductal gray

PANSS - Positive and negative syndrome scale

PD - Parkinson's disease

PFC - Prefrontal cortex

PLWC - Polydextrose, lactoferrin and whey protein concentrate

PND – Postnatal day

PNS - Peripheral nervous system

POMS - Profile of mood states scale

PPI – Prepulse inhibition

PrL - Prelimbic cortex

PS1 – Presenilin 1

PSD95 - Postsynaptic density protein 95

PSS - Perceived stress scale

PVN - Paraventricular nucleus

RANTES - Regulated on activation, normal T cell expressed and secreted

REM – Rapid eye movement

RMS - Resistant maize starch

RNA - Ribonucleic acid

RPS - Resistant potatoes starch

RVIP - Rapid visual information processing

SCFA – Short-chain fatty acid

sCSDS - Subchronic social defeat stress

SD - Sleep deprivation

SGZ - Subgranular zone

SIT - Social interaction test

SPF – Specific pathogen free

SPT – Social preference test

SYN – Synuclein

TBI – Traumatic brain injury

TDO - tryptophan 2,3-dioxygenase

Thy1 - Thymidylate synthase complementing protein 1

TNBS - 2,4,6-trinitrobenzene sulfonic acid

TNF-α/β - Tumor necrosis factor alpha/beta

TPH - Tryptophan hydroxylase

TRP – Tryptophan

TrkB - Tropomyosin receptor kinase B

TRPV1 - Transient receptor potential vanilloid 1

TST – Tail suspension test

TUNEL - Terminal deoxynucleotidyl transferase dUTP nick end labeling

VTA - Ventral tegmental area

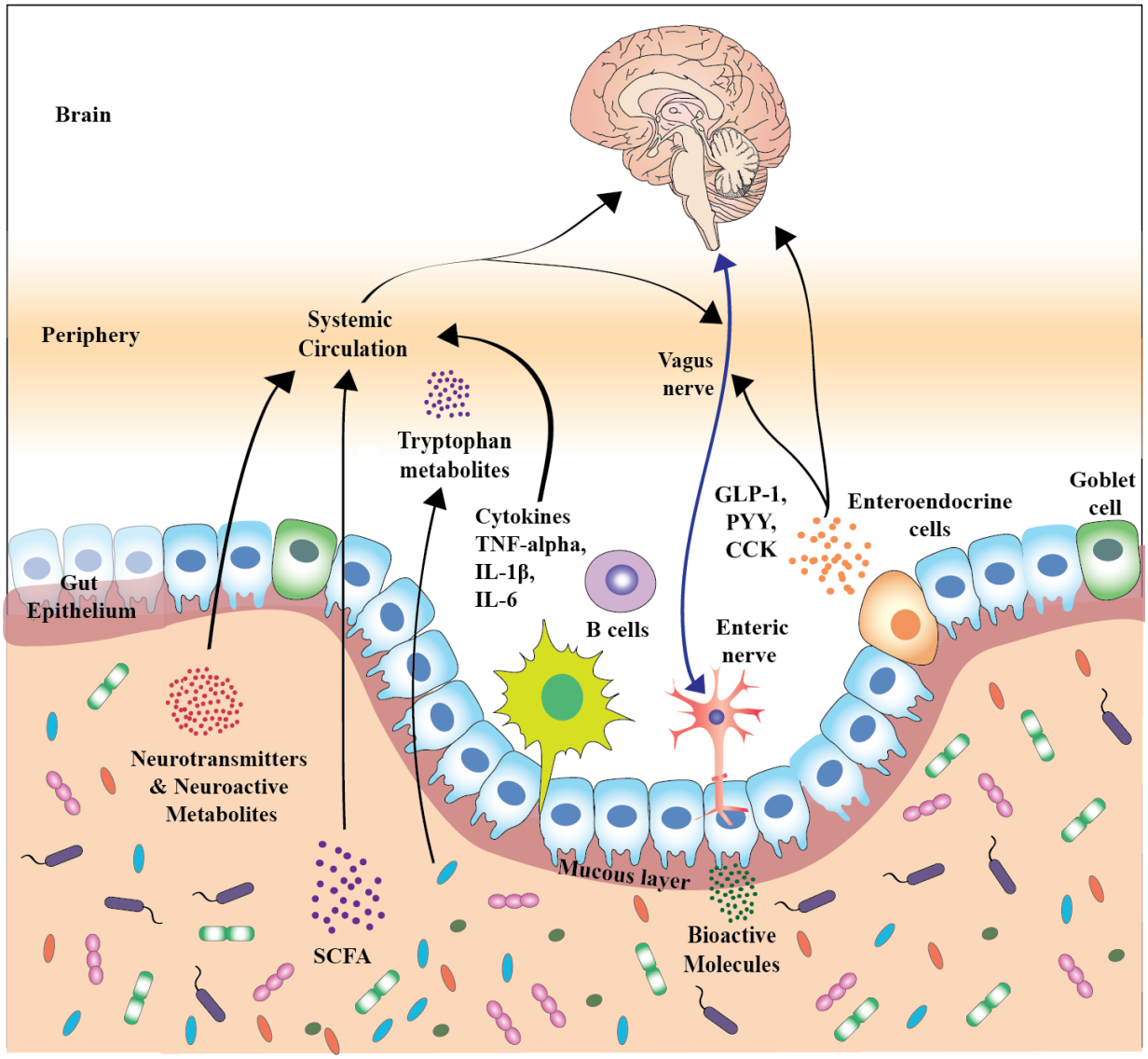
WAS - Water avoidance stress

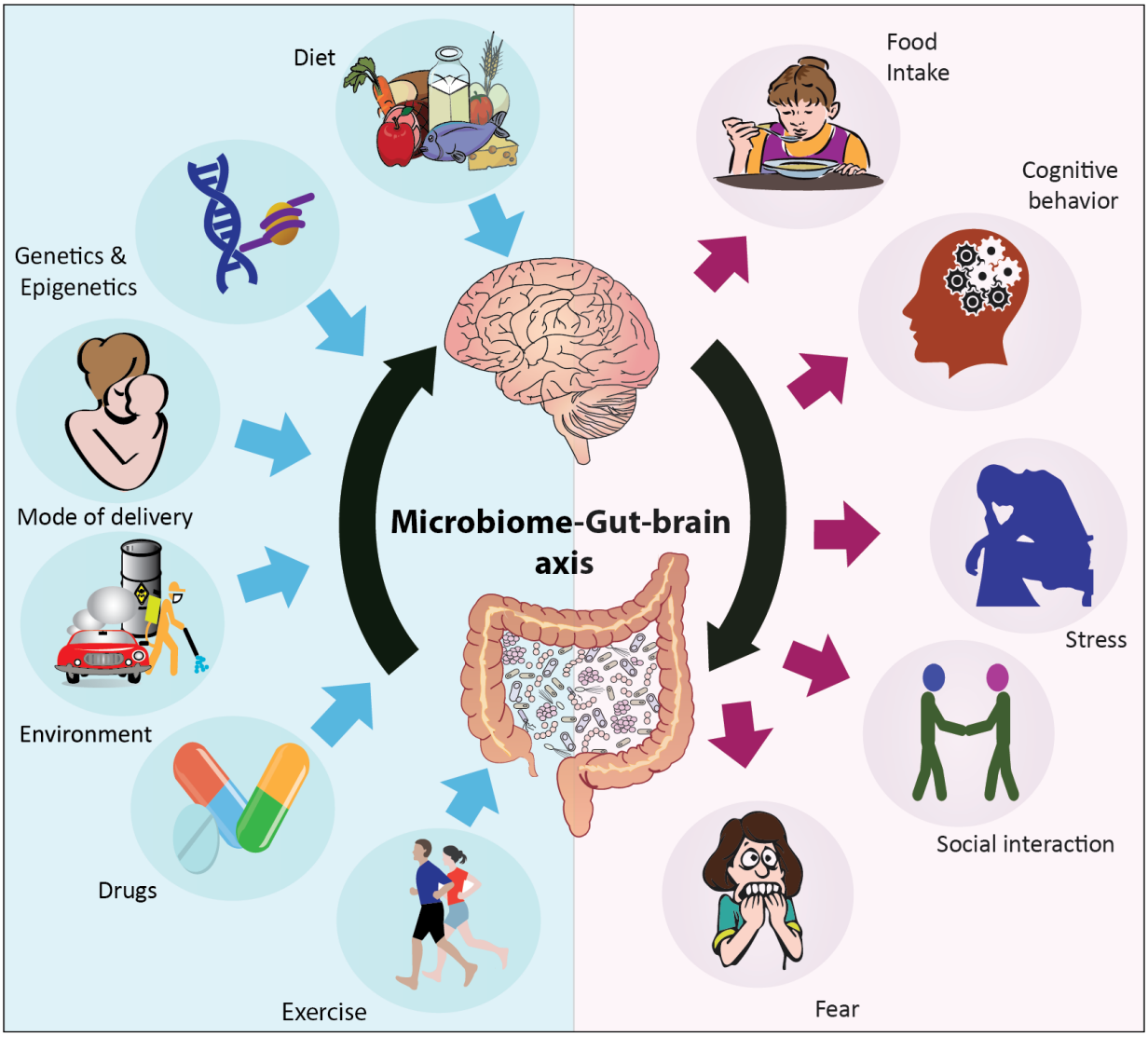
WKY - Wistar Kyoto

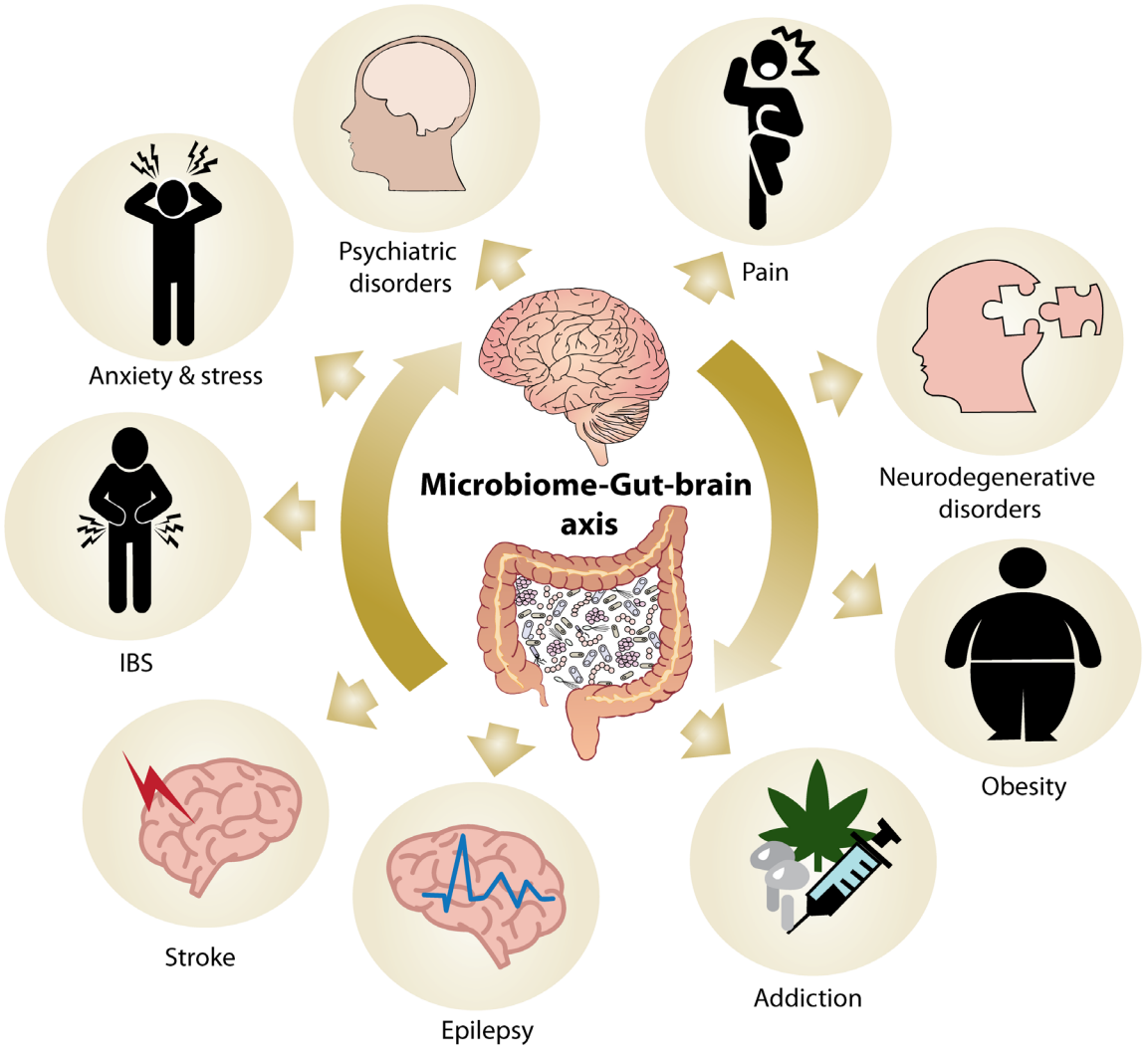
Call out box

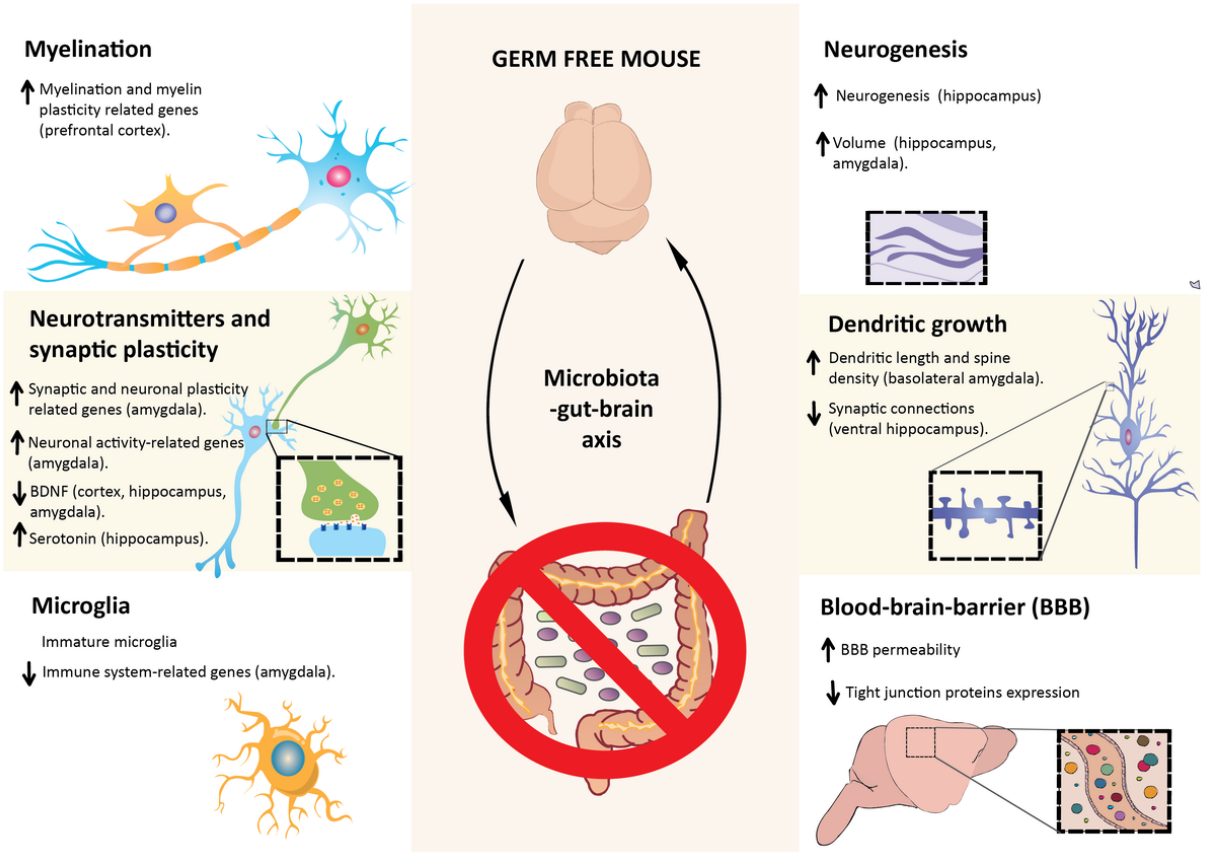
“This is a comprehensive review of current knowledge of the influence that the microbiota has on brain and behaviour. In particular we focus on the pathways involved and the models used in the field. Moreover, we highlight what still remains to be understood in order to fully realize the potential for the development of microbiota-based therapeutic strategies for brain disorders.”

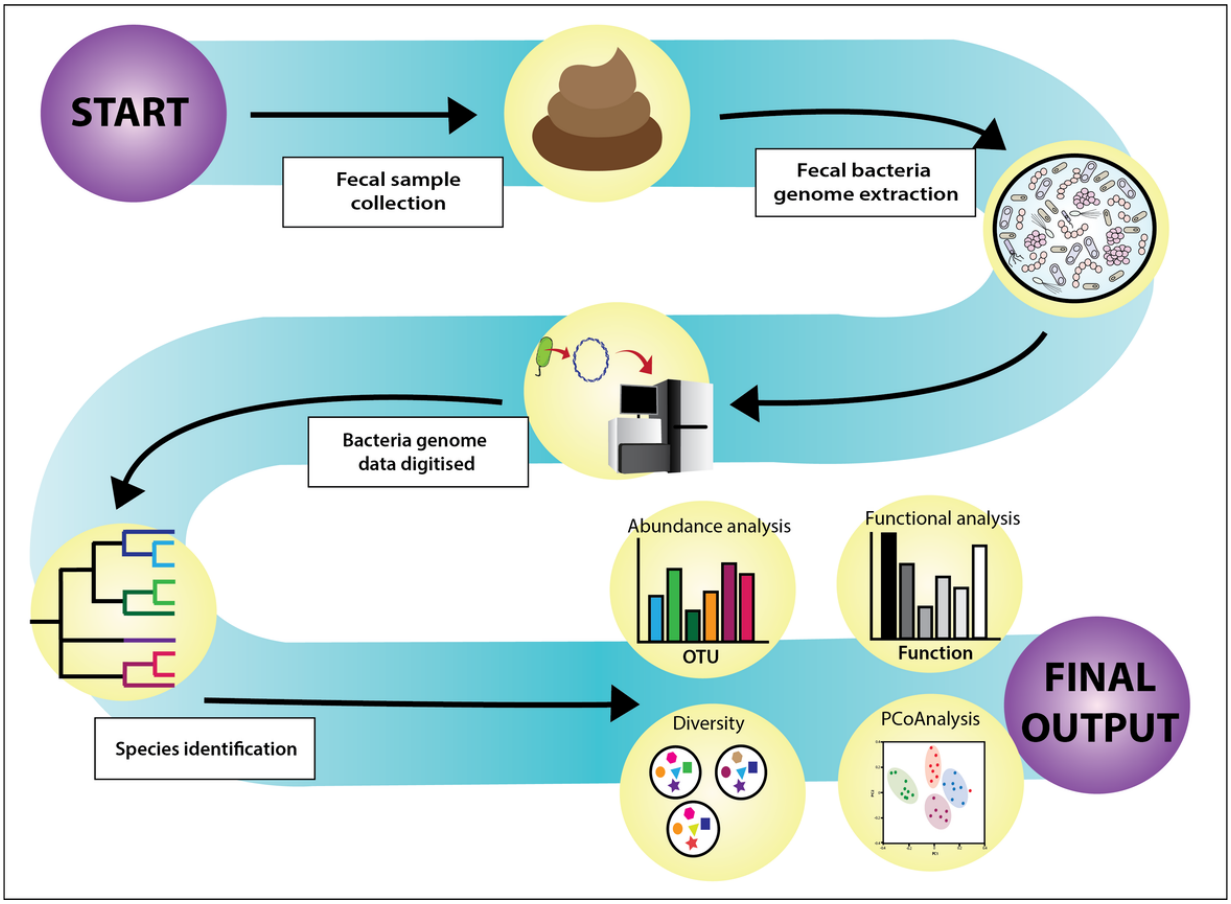
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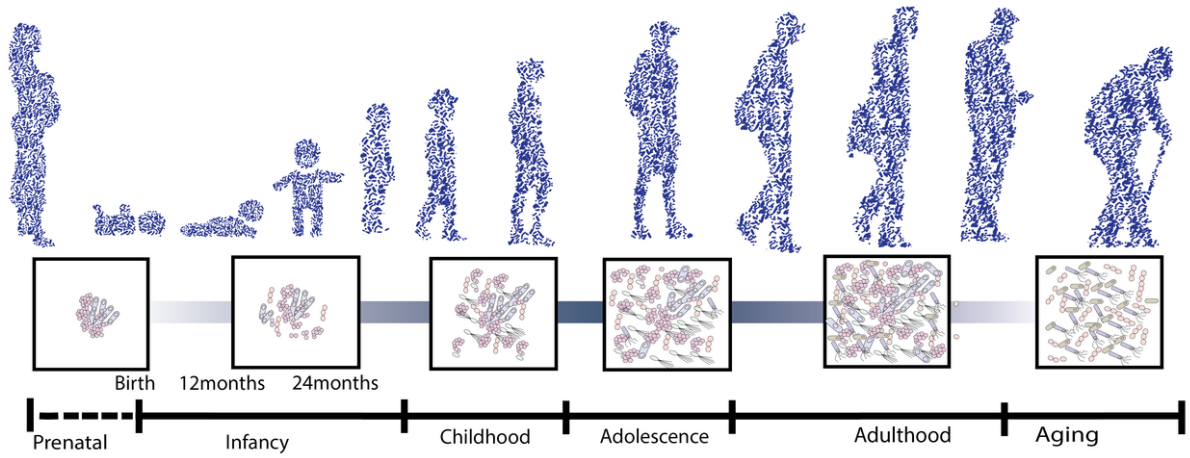

Brain
Periphery
Systemic Circulation
Vagus nerve
Tryptophan metabolites
Cytokines TNF-alpha, IL-1β, IL-6
GLP-1, PYY, CCK
Enteroendocrine cells
Goblet cell
Gut Epithelium
B cells
Enteric nerve
Neurotransmitters & Neuroactive Metabolites
Mucous layer
SCFA
Bioactive Molecules


Diet
Genetics &
Epigenetics
Mode of delivery
Environment
Drugs
Exercise
Microbiome-Gut-brain
axis
Food
Intake
Cognitive
behavior
Stress
Social interaction
Fear


Psychiatric disorders
Pain
Anxiety & stress
Neurodegenerative disorders
Microbiome-Gut-brain axis
IBS
Obesity
Stroke
Addiction
Epilepsy


Myelination
Myelination and myelin plasticity related genes (prefrontal cortex).
GERM FREE MOUSE
Neurogenesis
Neurogenesis (hippocampus)
Volume (hippocampus, amygdala).
Neurotransmitters and synaptic plasticity
Synaptic and neuronal plasticity related genes (amygdala).
Neuronal activity-related genes (amygdala).
BDNF (cortex, hippocampus, amygdala).
Serotonin (hippocampus).
Microbiota -gut-brain axis
Dendritic growth
Dendritic length and spine density (basolateral amygdala).
Synaptic connections (ventral hippocampus).
Microglia
Immature microglia
Immune system-related genes (amygdala).
Blood-brain-barrier (BBB)
BBB permeability
Tight junction proteins expression





Stages of brain development

neuronal proliferation
dendritic arborization
neuronal migration
neuronal loss
synaptic loss
apoptosis
synaptogenesis and synaptic refinement
excitatory synapses
inhibitory synapses
axonal growth and myelination