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Review

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REVIEW

Making Sense of … the Microbiome in Psychiatry

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Abstract

Microorganisms can be found almost anywhere, including in and on the human body. The collection of microorganisms associated with a certain location is called a microbiota, with its collective genetic material referred to as the microbiome. The largest population of microorganisms on the human body resides in the gastrointestinal tract; thus, it is not surprising that the most investigated human microbiome is the human gut microbiome. On average, the gut hosts microbes from more than 60 genera and contains more cells than the human body. The human gut microbiome has been shown to influence many aspects of host health, including more recently the brain.

Several modes of interaction between the gut and the brain have been discovered, including via the synthesis of metabolites and neurotransmitters, activation of the vagus nerve, and activation of the immune system. A growing body of work is implicating the microbiome in a variety of psychological processes and neuropsychiatric disorders. These include mood and anxiety disorders, neurodevelopmental disorders such as autism spectrum disorder and schizophrenia, and even neurodegenerative disorders such as Alzheimer's and Parkinson's diseases. Moreover, it is probable that most psychotropic medications have an impact on the microbiome.

Here, an overview will be provided for the bidirectional role of the microbiome in brain health, age-associated cognitive decline, and neurological and psychiatric disorders. Furthermore, a primer on the common microbiological and bioinformatics techniques used to interrogate the microbiome will be provided. This review is meant to equip the reader with a primer to this exciting research area that is permeating all areas of biological psychiatry research.

Keywords: microbiome, microbiology techniques, gut-brain-axis

Introduction

When the Dutchman Antonie van Leeuwenhoek peered through his homemade microscope in the seventeenth century, he dubbed the *kleine diertjens* (tiny animals) he found there *animalcules* (Lane, 2015). The discovery that microorganisms are residing practically everywhere, including in and on humans, had a profound impact on medical knowledge. A short time later, the link between these *small*, *bloodless animals* and a diarrhea epidemic was suggested by Valk (Valk, 1745). In 1890, Robert Koch published his famous postulates in an attempt to formulate criteria that would establish whether a given microbe causes a given disease (Koch, 1876). Up until recently in medicine, we have regarded microorganisms as undesirable germs to be kept at bay. They were thought to range from pathogenic to harmless to humans and relevant to almost all areas of medicine.

Nonetheless, the disciplines of microbiology and psychiatry evolved along distinct trajectories with only a few notable

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exceptions. Infamously, the psychiatrist Henry Cotton had the teeth of psychiatric patients in his care removed, believing microbes on their teeth to be the source of their illness (Anderson et al., 2017). There is also a report in the *British Journal of Psychiatry* in 1910 of the successful treatment of melancholia with *Lactic acid bacillus* (Phillips, 1910). An early adopter of the idea of microorganisms as beneficial was the 1908 winner of the Nobel Prize in Physiology and Medicine, Metchnikoff. He was convinced of the beneficial effects of fermented milk for "autointoxication" (a rather broad term encompassing a range of negative health outcomes, including fatigue and melancholia; Bested et al., 2013), so much so that it has been reported that he drank fermented milk daily. Despite Metchnikoff's early hypotheses regarding the potential health benefits of certain bacterial strains, these ideas were largely ignored for the better part of a century.

However, in the last decade, developments in sequencing technology and bioinformatics have allowed in-depth investigations into the composition of complex microbial ecosystems as well as the metabolic and metagenomic potential of such systems. Ventures like MetaHIT (Qin et al., 2010), the Human Microbiome Project (Methé et al., 2012), the ELDERMET study (Claesson et al., 2012), the Belgian Flemish Gut Flora Project (Falony et al., 2016), and the Dutch LifeLines-DEEP (Tigchelaar et al., 2015) have shed light on the bidirectional relationship between microorganisms and their hosts. This marks a pivotal change in our view of microbes. Not only do we now view microorganisms as a cause of disease, they are also increasingly seen as a cause of health (Bloomfield et al., 2016).

The largest population of microorganisms on the human body resides in the gastrointestinal tract. Known as the gut microbiota, this complex ecosystem is comprised of microorganisms including bacteria, fungi, and archaea from over 60 genera (Falony et al., 2016). Recent estimates put the total bacterial count on an average human at around 3.0×10^{13}, which is just more than the estimates of human cells in the body (Sender et al., 2016). In a 70-kg individual, the human gut microbiota would weigh in at an impressive 0.2 kg (Sender et al., 2016). The total genetic material of this mass is known as the microbiome. In terms of genes we are more than 99% microbial, meaning the vast majority of both genes and DNA found in a human originates from microbes (Qin et al., 2010). Perhaps the most surprising development to arise from this field has been the realization that the microbiome plays a key role in the programming of all major body systems, including the brain (Round and Mazmanian, 2009; Diaz Heijtz et al., 2011; Collins et al., 2012; Cryan and Dinan, 2012; Foster et al., 2016; Kundu et al., 2017).

In this review, an overview of our knowledge on the microbiome in relation to the brain will be provided. First, the development and function of the microbiome will be discussed in the context of health and well-being. Next, we will provide the reader with a summary of tools used to investigate the microbiome. Finally, the focus is brought to evidence for the role of the microbiome in states of stress and disease, including psychiatric disorders, age-associated cognitive decline, and neurological disorders. To aid the reader, a glossary is included (see Box 1). The overall goal of this review is to highlight the need to further study and better understand the microbiome, particularly with respect to its role in psychiatric health and disease. Not only does the microbiome represent a tremendously valuable therapeutic target for numerous psychiatric illnesses, but it is also a promising target for the general improvement of physical, mental, and cognitive states in healthy individuals.

The "Healthy" Microbiome

It is worth reminding ourselves that we are living in a microbial world; microbes were here first and there has never been a time when the brain existed without microbes (Stilling et al., 2014). It makes sense to consider the human host in the context of its environment. While scientific reductionism is a powerful tool, a more holistic systems biology approach has enabled us to more accurately understand complex interactions (Sugihara et al., 2012). In this spirit, the term holobiont, describing the totality of the host and its microorganisms, has gained increasing traction in the field (Bordenstein and Theis, 2015; Theis et al., 2016). By blurring the borders between otherwise clearly defined organ systems, the holobiont provides a useful concept for understanding the many levels of interaction between the host and its microbiome.

Where It Began

The composition of the microbiome is not only unique to each individual but is also known to differ drastically throughout the host's lifespan. For the most part, colonization of the human gut microbiome is thought to begin at birth, although this notion has become subject to debate based on recent reports of microbial DNA in the placenta and meconium (Stout et al., 2013; Aagaard et al., 2014). While these reports remain controversial (Perez-Muñoz et al., 2017), what is clear is that the neonate is exposed to the vaginal microbiome of the mother during delivery through the birth canal. In contrast, when the newborn is delivered via Caesarean section (C-section), it is exposed to the skin microbiome rather than the vaginal microbiome (Chu et al., 2017). Consequently, the microbiome of children delivered via C-section differs significantly from that of children delivered vaginally (Dominguez-Bello et al., 2010; Dominguez-Bello et al., 2016). Other factors, such as prematurity, breastfeeding, the presence of pets, parental smoking, maternal age, weight (especially obesity), and race are also known to impact the developing microbiome (Borre et al., 2014; Bokulich et al., 2016; Levin et al., 2016).

They Are What You Eat

As the infant develops, it seems that some of these early factors become less influential. For example, the microbiota of infants born by C-section or natural delivery converges over time, becoming indistinguishable by 6 weeks of age (Chu et al., 2017; Hill et al., 2017). However, one factor that continues to have a significant impact on microbiota composition throughout the lifespan is the diet of the host (David et al., 2014; Sandhu et al., 2017). In particular, the research shows a stark contrast between the Western diet, with its high sugar, animal fat, and carbohydrate content, in comparison to a Mediterranean diet, which is characterized by increased variety of foods and higher fiber content. The microbiota profile of individuals with these different diets is drastically different (Wu et al., 2011; De Filippis et al., 2016). Although previous studies have segregated different mammalian gut microbiomes based on their compositions, known as enterotypes, this concept has been challenged and is still in the process of being refined (Costea et al., 2018). While there is still debate over the canonical number of enterotypes in humans, there is a general consensus that a division can be made between an enterotype enriched at the genus level in *Prevotella* and one enriched in *Bacteroides*. Strikingly, this difference can be related to dietary intake. Specifically, fiber-rich diets are associated with

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Box 1. Glossary of microbiome-associated terms

Term	Definition
16S rRNA gene/transcript sequencing	Bioinformatics technique where highly conserved regions of the 16S rRNA gene (DNA) or transcript (cDNA) are used to identify present or metabolically active microbes in a sample, respectively.
Alpha diversity, beta diversity, gamma diversity	Statistical terms used in ecology to describe variability of a dataset. Alpha diversity describes within-sample variability, while beta-diversity describes variability between samples. Gamma diversity is rarely used and describes variability between all samples in the dataset. Many different formulas are available that define diversity differently, putting different weights on aspects like the number of species, how rare/abundant the species are, binary presence/abundance, and even taxonomic distance between species.
Enterotype	Name for a controversial type of microbiome classification based on the proportions of certain microbes.
Fecal microbiota transplantation (FMT)	Treatment where subjects are colonized with processed fecal matter (usually from a healthy donor in clinical cases or from a specific clinical population of interest in experimental studies). To ensure grafting of the donor microbiome, antibiotics (or germ-free animals) are generally used to deplete the recipient microbiome prior to FMT.
Flux balance analysis (FBA)	Computational technique used to predict the metabolic behavior of an organism. In other words, what metabolic pathways will be more or less active in an organism in a given environment.
Germ-free (GF)	A host without a microbiome. Generally refers to mice and rats that were born and reared in a sterile environment to keep them from developing a microbiome, for the purpose of experimentation.
GreenGenes, SILVA, RDP	Sequence databases and tools used to identify which microbes are present in a sample and their taxonomic relationships.
Holobiont	Term describing the collection of a host and its microbiomes.
Host	The organism (e.g., human, rodent etc.) that houses a given microbiome population.
Microbiome	A term often used synonymously with "microbiota" but more precisely used to refer to the collective genome of a given microbiota.
Microbiota	The collection of microorganisms found in/on a particular environment or living host.
PICRUSt, HUMAnN2, LEfSe, GraPhlAn, MetaPhlAn	Parts of the bioBakery set, software tools developed by the Huttenhower lab, used to analyze microbiome data. (https://bitbucket.org/biobakery/biobakery/wiki/Home)
Prebiotics	Nondigestible foods (such as fibers) that have a beneficial effect on the microbiome for the host.
Principal coordinate analysis (PCoA)	Statistical method used for datasets with many numerical values per sample, like microbiota data. The complex data are algorithmically converted to simpler set of values, called principal coordinates, with the aim of explaining variation in the data. Useful for visualizing differences between microbiome samples. If a principal coordinate is large, this is an indication it is determining a large proportion of the observed variance in the data.
Probiotics	Live microbes that have a positive effect on host health when ingested in adequate quantities.
Psychobiotics	Targeted interventions of the microbiome to support mental or brain health.
QIIME, QIIME2	Quantitative Insights Into Microbial Ecology: Software tools used to analyze microbiome data.
Phylum->Class->Order->Family->Genus->Species->Strain	Increasingly granular taxonomic levels used to classify lifeforms. Frequently used in the microbiome field.
Synbiotics	Synergistic combination of prebiotics and probiotics. The aim is to optimize treatment effects by providing both the beneficial microbes and the nutrients they need to survive and colonize.
Whole genome shotgun sequencing	Bioinformatics technique where all DNA in a sample is sequenced to identify which microbes are present in a sample and their functional (metagenomic) potential. More expensive than 16S rRNA sequencing, but gives more reliable functional predictions.

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the *Prevotella* enterotype, reflecting the role of *Prevotella* species in production of hydrolases specialized for plant fiber degradation (Purushe et al., 2010). *Bacteroides*, on the other hand, are associated with the Western diet (Costea et al., 2018).

The Microbiota-Gut-Brain Axis

The gut microbiota is known to interact with the brain indirectly, in a bidirectional manner, most likely through a variety of pathways including vagal nerve stimulation, interaction with the immune system, and microbial production of human neurotransmitters (see Figure 1; Cryan and Dinan, 2012; Lyte, 2014; Yano et al., 2015; Schirmer et al., 2016; Kennedy et al., 2017). While the precise mechanisms of action remain unknown, evidence for bidirectional communication between the microbiome and the brain is clear and the impact striking.

Besides regulating brain function, the microbiome has also been shown to regulate the physical development of the brain (Dinan and Cryan, 2017b). For instance, hypermyelination of prefrontal cortex neurons has been observed in the brains of germ-free mice (Hoban et al., 2016). Moreover, the dendrites of neurons in the amygdala and hippocampus of germ-free mice are morphologically distinct from those in control mice (Luczynski et al., 2016b). In a recent study, mouse pups born from germ-free mothers were colonized with microbiota from either slow- or fast-growing human infants (Lu et al., 2018). Pups with microbiota from fast-growing infants showed an accelerated neuronal differentiation when compared with slow-growing humanized and germ-free pups. In addition, slow-growing humanized mice were found to exhibit more signs of neuroinflammation. Finally, the microbiota-derived molecule Pglyrp2, which was determined to cross the blood-brain barrier, has been shown to influence the protein expression profile in the germ-free mouse model (Arentsen et al., 2017).

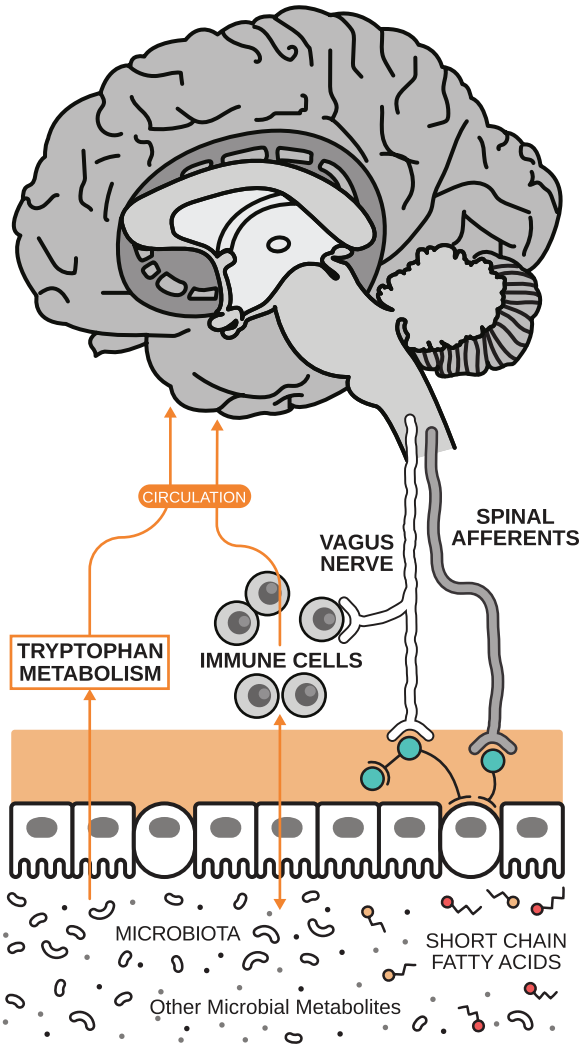

Figure 1. The gut-brain axis. Pathways of communication between the gut microbiome and the brain include vagal nerve stimulation, interaction with short-chain fatty acids, immunoregulatory elements, and tryptophan metabolism. In addition, certain microbes are known to produce and secrete human neurotransmitters. Figure adapted from Cowan et al. (2018).

Completing the circle, not only does targeting the gut microbiome influence the brain, there is research that suggests targeting the brain also influences the gut microbiome. There have been several recent studies indicating that certain pharmaceuticals, especially psychotropic agents, can shape the microbiome (Davey et al., 2012, 2013; Kao et al., 2018; Maier et al., 2018). The best evidence for psychotropic effects on the microbiota have been observed with antipsychotic drugs (Davey et al., 2012, 2013; Kao et al., 2018). In addition, most classes of antidepressants, including the widely used selective serotonin receptor inhibitors, have also been shown to impact the microbiota, exhibiting antimicrobial activity in vitro (Munoz-Bellido et al., 2000; Macedo et al., 2017). These findings are suggestive of a potential whole microbiota-gut-brain axis effect of certain psychotropics, consistent with the effects of stress and psychological state on this axis (Cryan and Dinan, 2012; Moloney et al., 2014; Foster et al., 2017). However, it is difficult to disentangle whether such effects are mediated by changes in signaling from the brain to the gut microbiota or, alternatively, via direct actions of the drugs on the microbiota. Other tools and models such as brain stimulation and traumatic brain injury are now being used to establish brain-to-microbiota influences more directly. Brain stimulation research is still very much in the preliminary stages; only one conference abstract on this topic has been published, which reported that deep transcranial magnetic stimulation improves symptoms of obesity by modulating gut microbiota (Ferrulli et al., 2018). In a controlled experimental model of stroke in mice, changes in the cecal microbiota were observed within 72 hours after brain damage was induced (Houlden et al., 2016). This work replicates clinical findings from a patient population of Chinese stroke victims who exhibited altered microbiota composition compared with asymptomatic controls (Yin et al., 2015). Together, these studies highlight the substantial influence of the brain over the microbiota, which we are only just beginning to understand.

Tools to Interrogate the Microbiome

Over the years, a plethora of different experimental models have been utilized to investigate the microbiome and its interactions with the host. Here, some of the most common will be discussed. For the most part, mice and rats are used as hosts when modelling the microbiome. While both animals have distinct features compared with humans, there are many similarities and advantages, making them the preferred models in most studies (Nguyen et al., 2015). However, many other species from drosophila (Leitão-Gonçalves et al., 2017) to zebrafish (Borrelli et al., 2016) and up to primates (Bailey and Coe, 1999; McKenney et al., 2015; Amaral et al., 2017) have also been used to investigate the microbiome. As the field of microbiota-brain

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interactions matures, we can expect that more studies will be carried out in healthy humans and clinical populations, which will further strengthen the conclusions that can be drawn from this line of research.

Microbiota Depletion: Germ-Free Animals and Antibiotics

As in all aspects of science and engineering, one of the main ways to confirm the importance of a specific process is to remove it and study the consequences. Germ-free animals represent our best available model for complete removal of all microorganisms. This method has been instrumental in linking the microbiome to many key brain processes and behaviors (Diaz Heijtz et al., 2011; Luczynski et al., 2016a, 2016b). However, given that germ-free animals exhibit such dramatically abnormal neurodevelopment, it is difficult to determine the precise role of the microbiome in said processes (Al-Asmakh and Zadjali, 2015; Luczynski et al., 2016a). Moreover, this is an extreme model with limited clinical translation.

While at first glance similar to the germ-free model, antibiotics represent an alternative distinct model to investigate the microbiome (Lundberg et al., 2016). Antibiotics have the advantage that they can be used to knock out/down the microbiota for specified timeframes without affecting neurodevelopmental programming per se. However, as antibiotic treatments can negatively impact the animals' health, it is sometimes hard to distinguish the side-effects of the antibiotics from the microbiome-driven effects (Luczynski et al., 2016a). Moreover, many antibiotics can cross the blood brain barrier (Nau et al., 2010), and caution is therefore required when interpreting studies of antibiotic-induced microbiota depletion.

"Friends with Benefits": Prebiotics, Probiotics, Synbiotics, and Psychobiotics

While disruption of the microbiome can have a negative effect on the host, supplementing the microbiome has been used as a strategy to optimize host performance. Introducing probiotic microbes that are known or suspected to be beneficial is an intuitive way to investigate the relationship between the host and the microbiome. Here, it is important to note that it is likely not just specific microbes that may be beneficial, but the collateral effects of that strain on the microbial ecosystem in given niches (Duran-Pinedo and Frias-Lopez, 2015). Although the term probiotic has gained substantial public attention and become part of the wider vocabulary, it is important to clarify that many commercially available strains marketed as probiotics have never been tested in clinical trials and therefore by definition would not meet the criteria of conferring a health benefit.

Prebiotics represent a more general way to alter microbiome composition, essentially providing nutrients to encourage the growth of beneficial microorganisms (Gibson et al., 2017). However, prebiotics are considered less specific than probiotics, as there is little control over which microorganisms will metabolize the prebiotics and which will proliferate. A growing body of work is now focused on combining prebiotics and probiotics to develop synbiotics (Ford et al., 2014). Finally, and most recently, the term psychobiotics has been introduced to describe targeted microbiome interventions with a beneficial effect on mental health, which is of particular interest to the study of psychiatric disorders (Dinan et al., 2013; Sarkar et al., 2016; Anderson et al., 2017). Overall, these approaches are appealing because they can be introduced in food and drink and therefore provide a relatively noninvasive method of manipulating the microbiota. While these studies show the potential of probiotics, negative studies have demonstrated that similar probiotic treatments can vary in effectiveness, suggesting that there are more factors at play than just the specific probiotic strain used (Hojsak et al., 2015, Mazurak et al., 2015). This conforms with the understanding that the behavior of a microbial strain is dependent on its metabolic, microbial, and host environment (Succurro et al., 2018).

Fecal Microbiota Transplantation (FMT)

The concept of fecal microbiome transplantation (FMT) as a therapeutic intervention is disrupting Western medicine completely. The procedure involves introducing fecal microbiota from a selected donor to the gastrointestinal tract of the recipient, with the aim of making the recipient microbiome more similar to that of the donor (Borody and Khoruts, 2011). When used as a therapeutic intervention, donors must be screened to ensure they are healthy, as phenotypes like obesity and depression have been shown to be transferable via FMT, at least in rodents (Turnbaugh et al., 2006; Kelly et al., 2016). FMT used in a preclinical setting can involve deliberately unhealthy donor phenotypes. The realization that patients with recurrent *Clostridium difficile* infection have a good chance to recover after FMT treatment represents an arguably noninvasive and cheap approach to an otherwise difficult to treat disease (Gianotti and Moss, 2017). Moreover, the potential of FMT as a clinical and experimental tool is reflected in the application of this approach to treat a wide variety of diseases (e.g., irritable bowel syndrome, steatohepatitis, ulcerative colitis, and even autism (Pinn et al., 2015; Ren et al., 2015; Kang et al., 2017; Zhou et al., 2017) and investigations of the effects of inter-species FMT from specific clinical populations to experimental rodents (Arrieta et al., 2016). Intriguingly, FMT from young donors to middle-aged recipients has even been used to extend the lifespan of killifish (Smith et al., 2017).

Cross-Sectional Studies

One of the most widely used methods to study the microbiome in humans is to assess microbiome composition across cohorts of clinical patients and matched controls. Thanks to the increasing number of such studies including the microbiome in their measurements, there are a large number of databases available for interrogation, such as the Human Pan Microbial Communities Database (Forster et al., 2016) and the NIH Human Microbiome Project (The N. I. H. H. M. P. Working Group et al., 2009). Here, it is important to note that it is often problematic to pool measurements from different databases together because the exact techniques used for extraction and processing of microbial genetic material account for a large part of the variation between samples (Clooney et al., 2016).

Analysis of the Microbiome

The field of bioinformatics is rapidly developing in response to the large amount of big microbiome datasets released thanks to Next Generation Sequencing (for a review of analysis techniques, see Claesson et al., 2017). Both 16S rRNA gene sequencing and whole genome shotgun sequencing techniques allow for analysis of compositional analysis and functional analysis of the microbiome (see Figure 2). It should be noted that because of the highly dynamic nature of the field, it is difficult to establish

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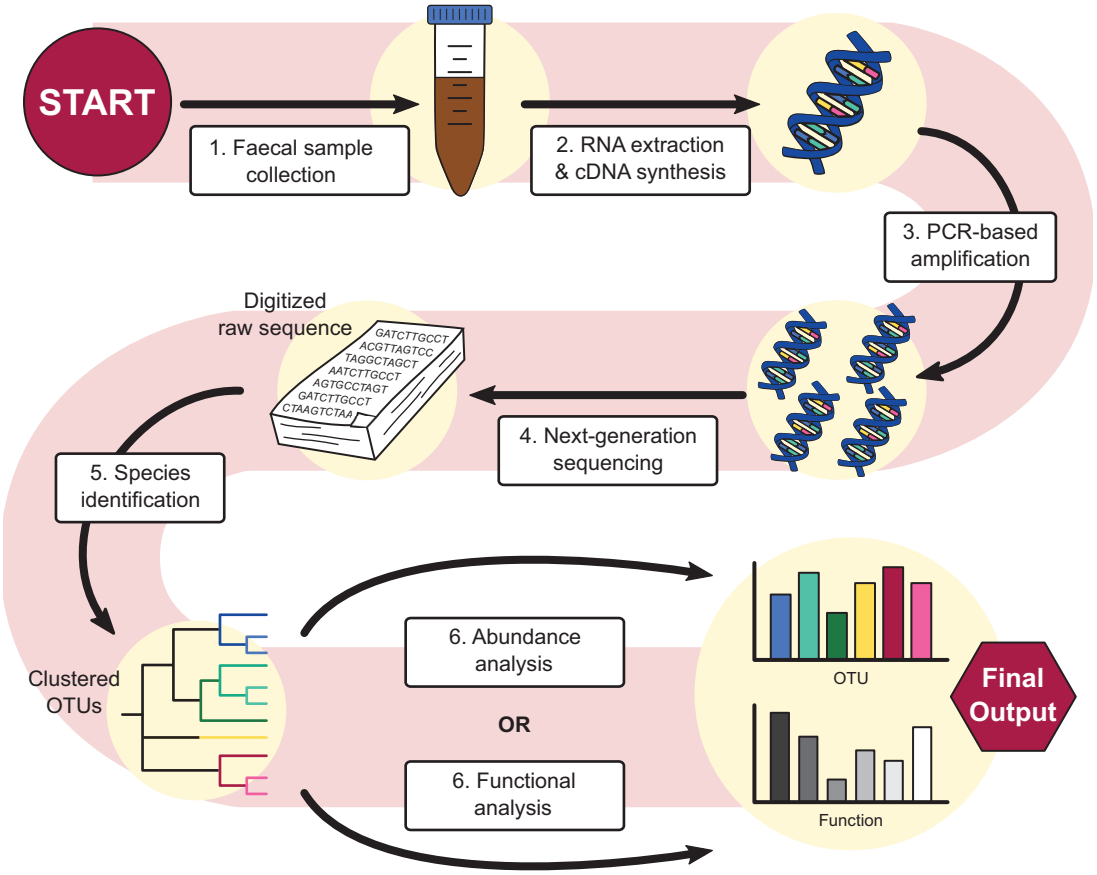

Figure 2. From stool to statistics. Overview of a sample method used to analyze the gut microbiome using 16S sequencing, a popular technique in microbiome research. Stool samples are collected and, potentially after being stored at -80°C, are prepared for analysis. RNA is extracted from the sample and a cDNA library is generated in preparation for amplification by PCR. Using next-generation sequencing platforms like Illumina and 454 pyrosequencing, the cDNA library is digitalized. From here, species can be identified by clustering the sequences and comparing them with a reference database. Popular databases for this purpose are RDP, SILVA, and, while arguably outdated, GreenGenes. The table of identified taxa can be used for abundance analysis and comparison using metrics like alpha diversity and beta diversity, principal coordinate analysis (PCoA) and differential abundance to quantify differences between samples or groups of samples on platforms like QIIME2. Using this same table, metagenomic data can be inferred, which can be used to make predictions about the functional implications of the observed differences in microbiome composition.

standard data-analysis protocols. Given the impact of both sequencing and in silico methods on the outcomes of analysis (Voigt et al., 2015; Clooney et al., 2016), we stress the importance of precise documentation when reporting microbiome research to ensure the reproducibility of findings.

Linking the Microbiome to Psychiatric Disorders

Given the many modes of communication between the brain and the gut microbiome, it is not difficult to imagine the impact the gut microbiome has on host mental health and illness. Here, we first discuss the role of the gut microbiome in stress regulation, as stress is one of the most potent risk factors for psychiatric illness. We then briefly discuss the current state of the evidence linking the microbiome to various psychiatric disorders, from developmental disorders to mood, anxiety, and eating disorders.

The Microbiome and Stress

There is a robust association between stress, which is associated with activation of the hypothalamus-pituitary-adrenal (HPA) axis, and the state of the microbiome (for reviews, see Moloney et al., 2014; Gur et al., 2015; de Weerth, 2017; Foster et al., 2017). A number of studies have demonstrated that stress alters the composition of the microbiota in a range of different hosts, from rats and mice (Gareau et al., 2007; O'Mahony et al., 2011; Golubeva et al., 2015; Bharwani et al., 2016; Burokas et al., 2017) to Syrian hamsters (Partrick et al., 2018), pigs (Mudd et al., 2017), and nonhuman primates (Bailey and Coe, 1999; Bailey et al., 2011).

In the other direction, the gut microbiome also regulates the stress response. In a seminal study, Sudo et al. (2004) elegantly demonstrated that germ-free mice exhibit elevated HPA axis responses to stress as measured by adrenocorticotropic hormone and corticosterone. The HPA axis response was found to be normalized by colonization with a probiotic species but exaggerated by colonization with an enteropathogen in the same study. Similarly, probiotics have been shown to reverse stress effects in many studies using various animal models (Gareau et al., 2007; Desbonnet et al., 2010; Bravo et al., 2011; Ait-Belgnaoui et al., 2012; Barouei et al., 2012; Liang et al., 2015; Cowan et al., 2016; Bharwani et al., 2017; Callaghan et al., 2016). Promisingly, there is analogous evidence that probiotics promote stress resilience or reduce stress-induced physical symptoms and cognitive deficits in humans (Diop et al., 2008; Langkamp-Henken et al., 2015; Kato-Kataoka et al., 2016; Allen et al., 2017; Wang, 2017; Papalini et al., 2018). Finally, certain prebiotics have also been

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shown to protect against stress-induced effects on the microbiome, physiology, and behavior (Tarr et al., 2015; Burokas et al., 2017).

Attention Deficit Hyperactivity Disorder (ADHD)

Diet has long been considered a potential predisposing factor for attention deficit hyperactivity disorder (ADHD; Jacobson and Schardt, 1999; Pelsser et al., 2011), and many studies testing the effects of elimination diets on symptoms of ADHD have produced positive outcomes (for reviews, see Jacobson and Schardt, 1999; Millichap and Yee, 2012). Of note, a Western-style diet is associated with increased risk for ADHD (Howard et al., 2011). Given the known influence of diet on the microbiome, it has been proposed that the association between diet and ADHD may be driven by the microbiome. Providing preliminary support for this hypothesis, altered microbiome composition has been observed in a clinical cohort of adolescents and adults with ADHD (Aarts et al., 2017). Using predictive functional analysis, it was found that these differences were likely to lead to differential regulation/synthesis of dopamine precursors, changes that were associated with decreased reward anticipation. Finally, one small longitudinal randomized control study of a perinatal probiotic intervention found that probiotic-treated children were less likely to be diagnosed with ADHD (Pärtty et al., 2015).

Autism Spectrum Disorder (ASD)

There is a strong relationship between autism spectrum disorders (ASD) and gastrointestinal disorders, including high rates of comorbidity between these seemingly disparate diagnoses (Hsiao, 2014) and evidence of a correlation between the severity of ASD and severity of gastrointestinal complaints (Adams et al., 2011). When examining the microbiome, several studies have observed differences in children diagnosed with ASD, including relatively low representation of members of the *Prevotella* genus and other fermenting microbes compared with typically developing children (Kang et al., 2013). While these correlative studies do not provide evidence of causality (Mayer et al., 2014), the case for investigating microbiome-based treatments for ASD continues to strengthen. One recent small-scale pilot study of FMT for ASD showed promising results (Kang et al., 2017), while perinatal probiotic treatment reduced the risk for ASD (Pärtty et al., 2015). Moreover, preclinical studies demonstrate the crucial role of the microbiota in many mouse models of autism (e.g., maternal immune activation, maternal high-fat diet, and the BTBR genetic model; Hsiao et al., 2013; Buffington et al., 2016; Golubeva et al., 2017) as well as specific symptoms of ASD such as abnormal social behavior (Desbonnet et al., 2014).

Schizophrenia

Recently, there have been calls to investigate the link between schizophrenia and the microbiome (Dinan et al., 2014; Severance et al., 2015). As in ASD, there are high rates of gastrointestinal problems reported in schizophrenia (Severance et al., 2015). This finding may be related to the proposed immune origins of the disorder (Patterson, 2009; van Kesteren et al., 2017) and provides a theoretical foundation for investigating the microbiome in schizophrenia, given the key role the microbiome plays in establishing and maintaining immune function (Hooper et al., 2012; Belkaid and Hand, 2014). A recent preliminary study of patients with first-episode psychosis identified differences in the microbiota composition, including reduced prevalence of *Lactobacillus* and *Bifidobacteria* species compared with healthy age-matched controls (Schwarz et al., 2018). Importantly, differences in the microbiota were correlated with severity of negative symptoms and risk for remission at 12-month follow-up but did not correlate with duration of antipsychotic drug treatment. Other studies have identified differences in the composition and functional potential of the oropharyngeal microbiome of individuals diagnosed with schizophrenia (Yolken and Dickerson, 2014; Castro-Nallar et al., 2015). Although probiotics have been proposed as a potential adjunctive treatment for schizophrenia, only one published study has examined the efficacy of this approach. Dickerson et al. (2014) found no effects of probiotic treatment on positive or negative symptoms, although the chosen probiotic (*Lactobacillus rhamnosus* GG and *Bifidobacterium animalis* subs. *lactis*) reduced the risk for severe bowel problems in a small group of outpatients with moderate to severe schizophrenia symptoms.

Bipolar Disorder

It has been proposed that microbiome-mediated immune activation may contribute to the onset of bipolar disorder (Dickerson et al., 2017). This hypothesis seems to have originated from the observation that patients with bipolar mania were approximately twice as likely as other patients to have been recently treated with systemic antibiotics (Yolken et al., 2016). Since then, evidence implicating the microbiota in bipolar disorder has started to build. The microbiome of bipolar patients has been found to differ from healthy controls, at least for patients with more severe symptoms (Evans et al., 2017). Specifically, significant differences in 2 separate genera of *Firmicutes* were observed (one being a reduction in *Faecalibacterium*, which has also been observed in major depression; see below), with these and several other genera correlating to symptom severity. Moreover, a recent pilot study has shown that probiotic supplementation reduces rates of rehospitalization in patients who have been recently discharged following hospitalization for mania (Dickerson et al., in press).

Major Depression

While the study of the microbiome in schizophrenia and bipolar disorder is still in its infancy, there is stronger (and continually mounting) evidence that the microbiome plays a role in major depression (Foster and McVey Neufeld, 2013; Dash et al., 2015). Germ-free mice display reduced depressive-like behavior; in the forced swim test of behavioral despair, germ-free mice will continue to swim or attempt to escape an inescapable pool for longer than control mice (Zheng et al., 2016), and both probiotic and prebiotic treatments have been shown to reduce depressive-like behavior in rodent models (Desbonnet et al., 2010; Bravo et al., 2011; Burokas et al., 2017). These studies seem to hold translational value, with several systematic reviews indicating that probiotics effectively improve mood in humans (Huang et al., 2016; Pirbaglou et al., 2016; Wallace and Milev, 2017). It is worth noting, though, that one such systematic review found that benefits were limited to those with mild to moderate depression (i.e., healthy individuals did not significantly benefit; Ng et al., 2018), which, alongside probiotic strain differences, may explain some of the conflicting findings in the attempts to translate probiotic effects to humans (Allen et al., 2016; Kelly et al., 2017).

Clinically, several studies have found an altered microbial composition in patients with major depression (Naseribafrouei et al., 2014; Jiang et al., 2015; Kelly et al., 2016;

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Zheng et al., 2016). Of note, 2 studies reported a reduction in the relative abundance of *Faecalibacterium* (Jiang et al., 2015; Zheng et al., 2016), mirroring the results described earlier for bipolar disorder (Evans et al., 2017). Jiang et al. (2015) went further to identify a negative correlation between the severity of depression and the prevalence of *Faecalibacterium*. Another study reported lower levels of *Bifidobacterium* and *Lactobacillus* in depressed patients (Aizawa et al., 2016). Strikingly, when the gut microbiome of depressed humans has been transferred to either rats or mice via FMT, the recipient animals exhibit greater depressive- and anxiety-like behavior compared with those that received FMT from healthy humans (Kelly et al., 2016; Zheng et al., 2016).

Anxiety Disorders

There is clear preclinical evidence to support a link between anxiety and the microbiome (Foster and McVey Neufeld, 2013; Malan-Muller et al., 2018). Germ-free mice and zebrafish exhibit reduced anxiety-like behavior (Diaz Heijtz et al., 2011; Neufeld et al., 2011; Clarke et al., 2013; Davis et al., 2016), although germ-free rats exhibit more anxiety-like behavior compared to conventionally colonized controls (Crumeyrolle-Arias et al., 2014). Anxiety-associated microbiome differences have also been observed between strains of mice, with the anxious BALB/c having a distinct microbiome profile compared with the more resilient Swiss Webster strain (Bercik et al., 2011). Furthermore, FMT from one mouse strain to the other was sufficient to partially transfer the respective behavioral phenotypes (i.e., BALB/c mice given NIH Swiss microbiota became less anxious, whereas NIH Swiss mice given BALB/c microbiota became more so).

Additional preclinical studies have shown that probiotic and prebiotic treatments can reduce anxiety-like behaviors in rodents (e.g., Bravo et al., 2011, Burokas et al., 2017). Unfortunately, very few studies have examined the relationship between anxiety and the microbiome in clinical populations. A single, small study of a South African population revealed specific phylum-level differences in the microbiome for those diagnosed with posttraumatic stress disorder compared with trauma-exposed controls (Hemmings et al., 2017). Aside from this correlational study, there have been 2 small intervention studies showing that probiotics reduce self-reported anxiety in healthy individuals (Messaoudi et al., 2011) and in a clinical group presenting with chronic fatigue syndrome (Rao et al., 2009).

Obsessive-Compulsive Disorders (OCD)

While there have been no direct investigations (as of yet) into the microbiome in obsessive-compulsive disorder (OCD) patients, several researchers have speculated that there may be a link (Rees, 2014; Turna et al., 2016). This hypothesis is based on 2 lines of observation. First, it has been noted that many of the risk factors for onset of OCD are also known to disrupt the microbiome, including stress, pregnancy, and antibiotic use (Rees, 2014). Second, there is preclinical evidence that OCD-like behavior in rodents (frequently measured using the marble burying test, which aims to assess repetitive, compulsive behaviors, one of the core symptoms of OCD) can be modified by microbial treatments, including germ-free environments and probiotic treatments (Nishino et al., 2013; Kantak et al., 2014; Savignac et al., 2014).

Eating Disorders

Perhaps unsurprisingly, given their highly impoverished nutrient intake, the microbiota composition of patients suffering from anorexia nervosa differs significantly from that of healthy individuals (Kleiman et al., 2015; Morita et al., 2015; Mack et al., 2016). In the first of these studies, by Kleiman et al. (2015), differences in anxiety, depression, and eating disorder psychopathology were all correlated to microbiota composition. Furthermore, microbiota composition changed during treatment and weight gain, moving closer to the composition observed in healthy control groups, although never fully recovering (Kleiman et al., 2015; Mack et al., 2016).

At the other end of the spectrum, the gut microbiome has also been linked to diet-induced obesity (Torres-Fuentes et al., 2017). Obese individuals exhibit differences in microbiota composition (Ley et al., 2005; Turnbaugh et al., 2006, but see also Sze and Schloss, 2016). Importantly, a causal contribution of the microbiome to diet-induced weight gain has been demonstrated using mice with a humanized microbiome (Turnbaugh et al., 2009). In these mice, switching from a plant-based diet to a Western-style diet caused rapid shifts in the microbiome composition (within 24 hours) and subsequent weight gain. Furthermore, the increased adiposity associated with the Western diet could then be transferred to naïve mice via FMT. Offering hope that we might utilize the microbiome to enact positive weight changes as well, it has been hypothesized that the microbiome may contribute to weight loss following bariatric surgery, based on evidence that such surgeries induce microbiome alterations in both humans and rodents (Peat et al., 2015; Torres-Fuentes et al., 2017).

In patients suffering from disorders that are associated with altered eating habits, it will continue to be difficult to disentangle the direction of microbiome-mental health relationships. It is intriguing to consider this problem; is eating behavior "manipulated" by an altered microbiome (as has been suggested by some, e.g., Alcock et al., 2014), does eating behavior drive microbiome changes and thereby alter gut-brain communication, or both? When considering this question, it is worth noting that changes in eating habits are not limited to eating disorders but are observed across a variety of psychiatric disorders (including anxiety, ADHD, ASD, depression; Yannakoulia et al., 2008; Ptacek et al., 2014), while epidemiological studies show that healthy dietary patterns are associated with better mental health (O'Neil et al., 2014). It is therefore an important question that deserves ongoing attention. Regardless of the initial cause of these disruptions, the opportunity to utilize dietary or other microbiome-targeting interventions to improve mental health holds great appeal and scientific potential.

Linking the Microbiome to Cognitive Impairment

The gut microbiome has been found to play a role in cognitive function, both in age-related cognitive decline as well as general cognitive performance. Mice that were treated with antibiotics showed decreased hippocampal neurogenesis (Möhle et al., 2016). Cessation of neurogenesis has been linked to general cognitive impairment and the onset of Alzheimer's disease (Costa et al., 2015; Hollands et al., 2017). FMT from healthy mice restored neurogenesis in the antibiotic-exposed animals, but only when combined with specifically selected probiotics (Möhle et al., 2016). In patients suffering from hepatic encephalopathy, where the patient exhibits neuropsychiatric abnormalities as a result of liver dysfunction, the presence and concentration of certain microbes was correlated to the severity of cognitive impairment (Bajaj et al., 2011).

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Just as development in early life has been found to parallel gut microbiome development, several age-related diseases have been similarly linked to the state of the microbiome in both animals (Scott et al., 2017) and humans (Claesson et al., 2012). In a study in elderly Koreans, administration of *Lactobacillus helveticus* IDCC3801 improved performance in cognitive fatigue tests (Chung et al., 2014). A decline in microbial diversity is associated with a concomitant increase in microglial activation correlated to brain mass differences in the mouse (Von Bernhardi et al., 2015). This contributes to an age-associated inflammatory response known as inflammaging, which in turn has been associated with neurodegenerative diseases such as Alzheimer's and Parkinson's diseases (Franceschi et al., 2007). Furthermore, the microbiome has been shown to regulate microglia activation; one study showed that germ-free mouse brains expressed defective microglia, which was partially rescued upon restoration of the microbial community to control levels (Erny et al., 2015; Möhle et al., 2016; Thion et al., 2018).

Linking the Microbiome to Neurological Disorders

Alzheimer's Desease (AD)

In addition to being involved in the general phenomenon of inflammaging, the gut microbiome has also been found to be involved in specific age-related illnesses. In patients with Alzheimer's disease (AD), Hill et al. (2014) reported a correlation between colonization of certain pathogenic microbes such as *Toxoplasma* and *Clamydophila pneumoniae* and progression of the disease. Furthermore, patients suffering from AD were shown to have a less diverse microbiome with distinct compositional differences compared with the healthy microbiome (Vogt et al., 2017). In the same study, the researchers theorized about the high prevalence of proinflammatory, lipopolysaccharide-producing, gram-negative bacteria such as *Bacteroides* in AD patients and their role in pathogenesis of the disorder (Cattaneo et al., 2017). Finally, germ-free or antibiotic-treated transgenic AD mouse models fail to develop plaques (Harach et al., 2017; Minter et al., 2017).

Parkinson's Disease (PD)

There is a growing emphasis on the role of the gut-brain axis in the onset of Parkinson's disease (PD; Dinan and Cryan, 2017a; Perez-Pardo et al., 2017). A number of studies have shown alterations in the microbiome in PD (Scheperjans et al., 2015; Keshavarzian et al., 2015; Heintz-Buschart et al., 2018; Qian et al., 2018; Sun et al., 2018). When mice were colonized with the microbiota of PD patients via FMT, they developed motor deficits and neuroinflammation, 2 hallmark symptoms of PD (Sampson et al., 2016). Additionally, symptoms improved when the mice were treated with antibiotics. Large-scale investigations using the extensive patient records in Denmark and Sweden have shown that vagotomy (or more specifically truncal vagotomy), which removes one of the major routes for microbiota to brain communication, is protective against PD (Svensson et al., 2015; Liu et al., 2017).

Multiple Sclerosis (MS)

The immune-related neurological disease multiple sclerosis (MS) has been convincingly linked to alterations in the microbiome (Berer et al., 2011; Wang and Kasper, 2014; Tremlett and Waubant, 2018). When the microbiome of patients diagnosed with MS was transferred to mice, the animals began exhibiting autoimmune encephalomyelitis, a main symptom of MS (Berer et al., 2017). Certain specific microbial species, like *Akkermansia muciniphila* and *Acinetobacter calcoaceticus*, have been identified that are present at significantly higher levels in patients suffering from MS than in the healthy population (Cekanaviciute et al., 2017). When these strains were introduced to mice, they again exhibited symptoms of autoimmune encephalomyelitis.

Conclusions

There are many ways in which the microbiome is connected to brain health. Oftentimes, it is hard to differentiate where the causative elements lie: in the brain or in the gut or in other systems such as the immune system. Therefore, it is not advisable to regard the two organs as separate systems but rather as a vastly more complex ecosystem of molecules, microbes, and neurons that should be approached with an interdisciplinary *modus operandi*. In the context of health and disease, the role of the microbiome as an ecological entity should not be ignored. Many afflictions discussed here are accompanied by alterations in the composition, or even stability, of the microbiome. Rather than the effect of individual taxa in a vacuum, their role in maintaining homeostasis within the microbiome deserves more scientific attention. Recently the role of *guilds*, taxonomically distinct but functionally related microbes that are associated with metabolic roles of the microbiome, has been stressed (Banerjee et al., 2018). Reinforcing the important role of diet in maintenance of the microbiota-gut-brain axis, food intake, especially dietary fiber, plays an important role in stabilizing these guilds (Zhao et al., 2018). Dietary interventions are gaining momentum as a plausible and modifiable target for improving mental health via the microbiome (Jacka, 2017; Jacka et al., 2017).

Considering the numerous illnesses that are impacted by the microbiome, it is hard to argue against further research to establish the precise underlying mechanisms involved. A comprehensive understanding of the mechanisms regulating the gut-brain axis in health and disease would be of tremendous benefit in predicting the efficacy of novel psychobiotics as well as potential off-target effects of traditional psychotropics. Developments in artificial intelligence and modelling seem promising in this regard. Techniques like flux balance analysis have been implemented to predict the growth medium required for 2 given microbiota to co-occur. There are still many challenges ahead of us, like how to handle the massive amounts of data that will be generated from mechanistic studies of the complex microbiome community.

For now, simply considering the role of the microbiome in a given disorder could be hugely beneficial. This would not only encourage us to keep up to date with current developments in microbiome research but will also help us understand and personalize treatments. After all, "just a gut feeling" seems to be more substantial than the saying might imply.

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