REVIEW SUMMARY

MICROBIOLOGY

Microbiota and the social brain

Eoin Sherwin, Seth R. Bordenstein, John L. Quinn, Timothy G. Dinan, John F. Cryan*

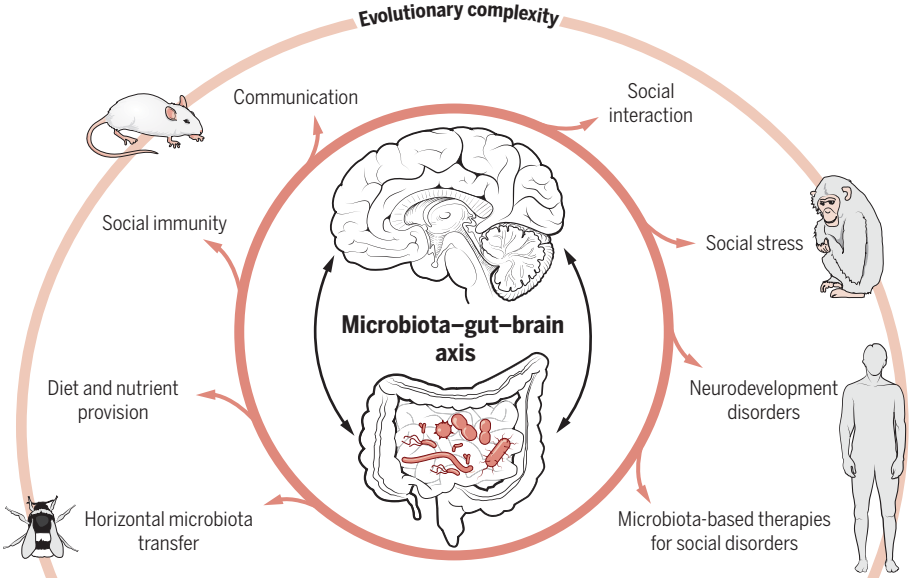
BACKGROUND: Increasingly, it is recognized that the microbes resident in the gastrointestinal tract can influence brain physiology and behavior. Research has shown that the gastrointestinal microbiota can signal to the brain via a diverse set of pathways, including immune activation, production of microbial metabolites and peptides, activation of the vagus nerve, and production of various neurotransmitters and neuromodulators in the gut itself. Collectively, this bidirectional pathway is known as the microbiota-gut-brain axis. In the absence of a microbiota, germ-free and antibiotic-treated mice exhibit alterations to several central physiological processes such as neurotransmitter turnover, neuroinflammation, neurogenesis, and neuronal morphology. Perhaps as a result of these neurological alterations, the behavior of rodents lacking a microbiota—especially social behavior—is remarkably different from that of rodents colonized with bacteria. Conversely, supplementation of animals with certain beneficial live bacteria (e.g., *Bifidobacterium* and *Lactobacillus*) can lead to notable improvements in social behavior both in early life and in adulthood. Collectively, these results suggest that microbial signals are important for healthy neurodevelopment and programming of social behaviors in the brain. Although research on the functional and ecological implications of the gut microbiota in natural populations is growing, from an evolutionary perspective it remains unclear why and when relationships between microbes and the social brain arose. We propose that a trans-species analysis may aid in our understanding of human sociability.

ADVANCES: Sociability comprises a complex range of interactive behaviors that can be cooperative, neutral, or antagonistic. Across the animal kingdom, the level of sociability an animal displays is variable; some are highly social (e.g., primates, termites, and honey bees), living within cooperative communities, whereas others have a mostly solitary existence (e.g., bears). Consequently, although studies on germ-free and antibiotic-treated animals have yielded insights into how the microbiota may influence social behaviors, they are perhaps too reductionist to fully appreciate the complex relationship between symbiotic bacteria in the gastrointestinal tract and host sociability when considering a broader zoological perspective. Some social interactions have evolved to facilitate horizontal transmission of microbiota. Observations across both invertebrate and vertebrate species suggest that factors such as diet and immunity generate selection pressures that drive the relationship between microbiota and social behavior. Although microbiota may influence behaviors endogenously through regulation of the gut-brain axis, some animal species may have evolved to use symbiotic bacteria exogenously to mediate communication between members of the same species. Hyenas, for example, produce an odorous paste from their scent glands that contains fermentative bacteria that is suggested to facilitate social cohesion among conspecifics. This complex relationship between animals and microbiota raises the hypothesis that microbes may have influenced the evolution of the social brain and behavior as a means to propagate their own genetic material.

ON OUR WEBSITE

Read the full article at http://dx.doi.org/10.1126/science.aar2016

OUTLOOK: Understanding the factors that affect the development and programming of social behaviors across the animal kingdom is important not only in terms of rethinking the evolution of brain physiology and behavior, but also in terms of providing greater insight into disorders of the social brain in humans [including autism spectrum disorders (ASDs), social phobia, and schizophrenia]. Evidence for a link between the microbiota and these conditions is growing, and preclinical and emerging clinical data raise the hypothesis that targeting the microbiota through dietary or live biotherapeutic interventions can improve the associated behavioral symptoms in such neurodevelopmental disorders. Larger clinical trials are required to confirm the efficacy of such interventions before they are recognized as a first-line treatment for neurodevelopmental disorders. Although such connections between gut bacteria and neurodevelopmental disorders are currently an intriguing area of research, any role for the microbiota in the evolution of social behaviors in animals does not supersede other contributing factors. Rather, it adds an additional perspective on how these complex behaviors arose. ■



The relationship between the microbiota-gut-brain axis and social behavior. The bidirectional pathway between the gut microbiota and the central nervous system, the microbiota-gut-brain axis, influences various complex aspects of social behavior across the animal kingdom. Some animals have evolved their own unique relationship with their gut microbiota that may assist them in interacting with conspecifics. The relationship between the gut microbiota and social behavior may help to explain social deficits observed in conditions such as autism spectrum disorders (ASDs) and could potentially lead to the development of new therapies for such conditions.

The list of author affiliations is available in the full article online.
*Corresponding author. Email: j.cryan@ucc.ie
Cite this article as E. Sherwin *et al.*, *Science* **366**, eaar2016 (2019). DOI: 10.1126/science.aar2016

REVIEW

MICROBIOLOGY

Microbiota and the social brain

Eoin Sherwin[1], Seth R. Bordenstein[2], John L. Quinn[3], Timothy G. Dinan[1,4], John F. Cryan[1,5]*

Sociability can facilitate mutually beneficial outcomes such as division of labor, cooperative care, and increased immunity, but sociability can also promote negative outcomes, including aggression and coercion. Accumulating evidence suggests that symbiotic microorganisms, specifically the microbiota that reside within the gastrointestinal system, may influence neurodevelopment and programming of social behaviors across diverse animal species. This relationship between host and microbes hints that host-microbiota interactions may have influenced the evolution of social behaviors. Indeed, the gastrointestinal microbiota is used by certain species as a means to facilitate communication among conspecifics. Further understanding of how microbiota influence the brain in nature may be helpful for elucidating the causal mechanisms underlying sociability and for generating new therapeutic strategies for social disorders in humans, such as autism spectrum disorders (ASDs).

In 1973, Konrad Lorenz, Niko Tinbergen, and Karl von Frisch won the Nobel Prize for their groundbreaking research concerning the origin, development, and elicitation of individual and social behavior patterns in animals. Their work provided a foundation for assessing the various intrinsic and extrinsic factors that affect social behavior. Enormous advances in understanding behavior have since been made, and social behavior in particular has grown to be one of the most intriguing and complex fields in organismal biology research (Fig. 1).

Social behavior can be defined as a behavior that is observed only when animals occur in a group. Some of these behaviors, such as cooperation, shared risk, empathy, and interdependence, are beneficial; others, such as conflict, dominance, and coercion, are costly (*1*). An understanding of the intrinsic and extrinsic factors that regulate social interactions is important for unraveling how individuals and populations thrive, for determining why some species of animals have evolved to be more sociable than others, and for elucidating the underlying etiology of social behavior disorders (*2*).

A new appreciation of host-microbe interactions has led to unprecedented focus on the microbial world in animals, both invertebrates (e.g., termites, honey bees, wasps) and vertebrates (birds, hyenas, humans). Pioneering research has identified influences of the gastrointestinal microbiota on health, including immunity, metabolism, cardiovascular function, hormonal production and secretion, reproduction, and longevity (*3*–*5*). The microbiota also seems to play a role in neurodevelopment from early life to adulthood and influences neurological processes such as neurotransmission, neuroinflammation, and behavior throughout an animal's lifespan (*6*–*9*). Microbe-derived signals may directly or indirectly alter brain function (*10*), and because animals evolved in a microbial world, these signals may have influenced animal brains throughout evolution.

Emerging research is now conceptualizing animals as "holobionts": dynamic ecosystems, comprising a host and its associated microorganisms, that can vary with time, localization, and function (*11*–*13*). Collectively, the host and microbial genomes of a holobiont are termed a hologenome, and variation in the hologenome caused by changes in the host and/or microbes may affect phenotypes that may be subject to natural selection (*11*). In some instances, this conceptualization may offer an integrative paradigm for explaining the evolution of social behaviors. Microbes influence host nervous systems (*8*) and are implicated in determining social cues in animals such as hyenas, mice, and fruitflies (*14*–*16*). Indeed, microbe-induced increases in social interactions can in principle facilitate the spread of microbes between hosts (*17*). Reciprocally, social organization and behavior may influence the microbiota composition within a group of animals (*18*). Therefore, the microbiota and social behavior are intertwined across the animal kingdom, and this has implications for how host-microbiota relationships may have evolved (*12*) as well as for the pathogenesis of human disorders of social behavior. In this review, we summarize the proposed mechanisms underlying links between the gut microbiota and the social brain, and describe the diversity of such connections across the animal kingdom. These links may help to explain why the microbiota is implicated in social disorders and how it can be targeted to influence brain health.

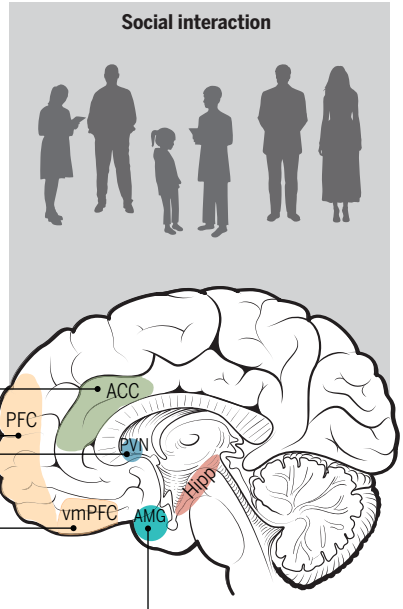
Mechanisms of microbiota-gut-brain communication

The concept that gut bacteria may influence brain physiology and behavior has existed for a long time. In 1910, the English physician George Porter Phillips proposed that major depression could be treated by the administration of a gelatin-whey formulation containing lactic acid bacteria (*19*). Currently evidence is accumulating that many behavioral responses observed across the animal kingdom might be regulated by the gut microbiota at various stages of an animal's life (Box 1). Within this paradigm, there is a growing emphasis on elucidating the mechanisms by which enteric bacteria communicate with the brain (Fig. 2). Such efforts are still in their infancy and are heavily focused on laboratory rodents. Nonetheless, a number of pathways of communication are particularly relevant to microbial influences on social behavior. These include activation of the vagus nerve, the production of microbial metabolites such as short-chain fatty acids (SCFAs) and neurotransmitters, the immune system, and sensory pathways such as the olfactory system (*8*).

Vagus nerve

The vagus nerve represents the main neural pathway connecting the gastrointestinal tract to the nucleus of the solitary tract (a cluster of afferent nerve fibers from the periphery that projects to regions of the neocortex such as the hypothalamus) in the brainstem in mammals (*20*). The nerve does not directly interact with the gut microbiota, although it may sense microbial signals through the release of various bacterial metabolites or through microbiota-mediated modulation of enteroendocrine cells in the gut epithelium (*21*). Indeed, vagal afferents have recently been shown to form synaptic connections with enteroendocrine cells in the gut, which facilitates the communication of nutritional signals to the brain via glutamatergic neurotransmission (*22*). Vagal nerve fibers are enriched with receptors such as 5-HT3, Toll-like receptor 4 (TLR4), free fatty acid receptors (FFARs), and gut peptide receptors; thus, they are ideally placed to transmit signals from the gut lumen to the brain (*21*). There is even preclinical evidence that the vagus nerve is capable of transporting proteins from the gut to the brain. For instance, in rats (*Rattus norvegicus*), α-synuclein, which forms aggregates in the brain in Parkinson's disease, was localized within the gastrointestinal system and transported from the gut to the brain via axonal transport by neurons contained

[1]APC Microbiome Ireland, University College Cork, Cork, Ireland. [2]Department of Biological Sciences, Vanderbilt Microbiome Initiative, Vanderbilt University, Nashville, TN, USA. [3]School of Biological, Earth and Environmental Sciences, University College Cork, Cork, Ireland. [4]Department of Psychiatry and Neurobehavioral Sciences, University College Cork, Cork, Ireland. [5]Department of Anatomy and Neuroscience, University College Cork, Cork, Ireland.
*Corresponding author. Email: j.cryan@ucc.ie



Anterior cingulate cortex (ACC)
This brain region functions in the detection and valuation of social processes such as interactions with dominant males and females in primates, and decision-making games in humans.

Prefrontal cortex (PFC)
In humans, this brain region is activated in response to various social cognitive tasks such as empathy, moral decision making, and judging the mental states of others. In rodents, stimulation of excitatory neurons abolishes social exploration and preference.

Paraventricular nucleus of the hypothalamus (PVN)
Magnocellular neurons of the PVN produce the neuropeptide oxytocin. Oxytocin is secreted to brain regions involved in sociability and social cognition, such as the ventral tegmental area and PFC. Reduced levels of oxytocin are documented in autism.

Ventromedial prefrontal cortex (vmPFC)
Lesions to this part of PFC result in social isolation and apathy in humans. The vmPFC is also important in the learning of cues that predict social reward. Children with ASD display reduced vmPFC activation in response to social reward.

Amygdala (AMG)
Amygdalar volume correlates with the size and complexity of social networks in humans. This brain region functions in the analysis of social situations. Individuals with autism demonstrate reduced activation of this brain region in response to social judgment tasks.

Fig. 1. Social behavior is governed by multiple interconnected limbic brain regions. Preclinical and clinical imaging studies have helped delineate the neurocircuitry underlying social behavior in humans and other mammals. Social interaction is governed by several subcortical forebrain structures such as the prefrontal cortex (PFC), anterior cingulate cortex (ACC), amygdala (AMG), hippocampus (Hipp), and hypothalamus (paraventricular nucleus, PVN), which form part of an integral interconnected network to facilitate this complex behavior. Damage or dysfunction to any one of these brain regions can give rise to perturbations in social behavior. Indeed, the neurobiology of regions such as the AMG and PFC have been shown to be altered in disorders of the social brain such as autism spectrum disorders (ASDs).

within the vagus nerve (*23*). Whether this influences the pathology and neuroinflammation observed in Parkinson's disease is unknown. However, there is a growing body of observational data in humans, from Danish and Swedish healthcare registries, that demonstrates an association between vagotomy (the surgical denervation of the vagus nerve) and a reduced risk for the development of Parkinson's disease (*24*).

Perhaps the most striking observation regarding the role of the vagus nerve in the microbiota-gut-brain axis comes from vagotomy studies in mice (*Mus musculus*). For instance, the ability of the bacterium *Lactobacillus rhamnosus* JB-1 to modulate anxiety-like behavior and γ-aminobutyric acid (GABA)–mediated neurotransmission in mice was lost after vagotomy (*25*). Similarly, the anxiolytic-like effects of the bacterium *Bifidobacterium longum* NCC3001 were absent in mice that underwent vagotomy (*26*). Moreover, *Lactobacillus reuteri*, a probiotic (live bacteria that when consumed confer health benefits to the host), increased the central expression and secretion of oxytocin (a hormone that functions in mammalian pair-bonding and is implicated in the neurobiological alterations reported to occur in ASDs) in mice, which was abrogated after vagotomy (*17*, *27*). However, not all microbial signals to the brain are mediated by the vagus nerve. Anxiety-like behavior in mice induced by a mild gastrointestinal infection was evident after vagotomy, which indicates that other biological pathways (some of which are known to be influenced by the microbiota) can mediate the anxiogenic effects of gastrointestinal infection (*28*).

Microbial metabolites

Gut microbiota are capable of producing a plethora of metabolites such as volatile carboxylic acids, esters, neurotransmitters (e.g., serotonin), and various fatty acids, some of which are implicated in influencing brain physiology and behavior. In vitro studies demonstrated that certain bacteria are capable of producing neurotransmitters such as noradrenaline, dopamine, and GABA (*29*–*31*). However, whether these gut-derived neurotransmitters are capable of reaching the central nervous system (CNS) to elicit an effect on their cognate receptors is unknown and unlikely considering their short half-lives and inability to cross the blood-brain barrier. The gut microbiota has indirectly been shown to influence serotonergic neurotransmission by regulating the availability of its precursor, tryptophan. Circulating tryptophan concentrations were found to be higher in male germ-free mice compared to controls with an intestinal microbiota (*32*). This corresponded with an increase in hippocampal serotonin and its metabolite, 5-hydroxy-indole acetic acid (*32*). Whether this has any bearing on the social deficits observed in these animals is unknown and requires further investigation.

Gut bacteria produce various SCFA metabolites such as butyrate, propionate, acetate, and valerate. These small molecules can regulate various physiological functions through their cognate FFARs. However, they may also mediate epigenetic modification through their histone deacetylase properties. FFARs are expressed on the vagus nerve, which partially mediates the effects of SCFAs. SCFAs have also been shown to influence certain central physiological processes. For instance, administration of a mixture of acetate, propionate, and butyrate was capable of restoring the morphological deficits of microglia (CNS-resident immune cells) that are observed in germ-free mice (*33*) and reversed the behavioral and physiological effects of chronic stress in mice (*34*). Moreover, SCFAs may influence the production of neurotransmitters in the brain through regulating the expression of enzymes involved in their biosynthesis. Administration of propionate and butyrate to PC12 cells (rat neuroblasts that differentiate into neuron-like cells) in vitro increased the expression of tyrosine hydroxylase, the rate-limiting enzyme in noradrenaline and dopamine synthesis (*35*). However, it is not clear whether these microbial metabolites are capable of regulating neurotransmission in vivo. Indeed, more evidence is needed to determine the extent to which physiologically relevant concentrations of SCFAs produced by the gut microbiota are capable of reaching the brain because they have short half-lives (25 min to 3 hours). To date, many studies investigating the effect of exogenous SCFA administration on brain physiology and behavior typically use concentrations that far exceed what is microbially derived (*36*).

Immune mechanisms

The immune system, by protecting the host against invading pathogens and internal damage, is fundamental for the survival of all species. Immunity also serves a critical role in mediating communication between the gut microbiota and the brain. The gut microbiota may influence the immune system locally at sites such as Peyer's patches (lymphatic nodules

Box 1. Modeling behavior and microbiota dysregulation.

Germ-free mice are completely devoid of microorganisms in and around their body and are raised in sterile isolator units to prevent their exposure to various bacteria, viruses, and fungi. In the absence of a microbiota, germ-free mice displayed deficits in social recognition and social cognition (*17*, *108*, *130*). Post-weaning reconstitution with gut microbiota restored the preference to interact with a conspecific mouse over an object or an empty chamber, but not the ability to discriminate between an unknown and a familiar mouse (*130*). These observations suggest that some facets of social behavior are amenable to manipulation by the microbiota, whereas others are not. However, in a separate study in germ-free mice, an increase in sociability and social cognition was observed in the absence of a gastrointestinal microbiota, contradicting other reports of decreased social behavior (*17*, *130*, *131*). Given that the strain of mouse and the animal supplier were the same between the studies observing a decrease (*130*) and an increase (*131*) in the sociability of germ-free mice, it is difficult to identify any discernible cause for the contrasting behaviors.

Despite these discrepancies, studies in germ-free mice have yielded insights into how gut bacteria influence brain physiology and behavior, with the amygdala being a brain region that is sensitive to microbiota manipulation (*8*, *25*, *132*, *133*). Transcriptional pathways linked to neuronal activation in the amygdala were increased in germ-free mice, indicating that the functionality of this brain region is altered in the absence of a microbiota (*133*). Furthermore, the expression of microRNAs linked to anxiety, stress, and the regulation of neurotrophins in the amygdala was affected in these animals and was somewhat restored after reconstitution with microbiota (*133*). In addition, the morphology of neurons within the amygdala of germ-free mice was altered, with an increase observed in the overall size of the various amygdalar subnuclei (*133*).

The use of antibiotics to deplete the microbiota has also been a successful strategy in unraveling the role of the microbiota in social behavior, with deficits observed in rodents after antibiotic administration from the adolescent period through to adulthood (*134*). Social recognition and cognition in mice were also affected after antibiotic administration (*135*). This effect of antibiotics on social behavior is not specific to rodents; a mixture of antibiotics also reduced social cohesion in zebrafish (*Danio rerio*) (*136*). Although studies using antibiotics have been beneficial in demonstrating a potential role for the gut microbiota in regulating social behavior, there are instances when this class of drug can facilitate sociability. The mechanism by which antibiotic administration modulates social behavior may be dependent on several variables such as preexisting gastrointestinal inflammation, baseline microbiota composition, diet, and stress perception. In invertebrate species, antibiotics can also affect cooperative behaviors. For example, diet-dependent mating of fruitflies (*Drosophila melanogaster*) was ablated after antibiotic administration but was subsequently reversed after supplementation with the gut bacterium *Lactobacillus plantarum* (*137*, *138*).

present in the small intestine that monitor gastrointestinal bacterial populations) or mesenteric lymph nodes. However, bacteria can also release various immune agonists such as lipopolysaccharide (LPS) and peptidoglycan (PGN) into blood circulation, where they might gain access to the brain. For example, neurons in the developing mouse brain express receptors that sense bacterial PGN (*37*). Germ-free and antibiotic-treated mice both display a reduction in the expression of several of the receptors that detect PGN in the striatum, which suggests that gene expression in the brain might be sensitive to microbiota manipulation. Moreover, knockdown of one of these PGN-sensing receptors, PGLYRP2 (PGN recognition protein 2), resulted in an increase in sociability in both male and female mice, indicating that loss of the ability to sense PGN results in behavioral changes to the host (*37*).

There is some preclinical evidence to suggest that the gut microbiota may influence development of the immune system, even in the CNS. For example, microglia isolated from the brains of germ-free mice display an immature phenotype compared with microglia from controls (*33*). Germ-free mouse–derived microglia demonstrated reduced activation in response to stimulation with bacterial LPS, with a concomitant reduction in the level of pro-inflammatory cytokine production (*33*). This observation was replicated after administration of antibiotics to mice and microglial functionality was restored in both scenarios after supplementation with SCFAs, which further corroborates a role for the gut microbiota in influencing the development of the immune system (*33*). The precise role that microglia play in social behavior is not completely understood. However, interference with microglial-neuronal communication (*38*) and depletion of microglia in early life (*39*) have both been shown to impair social behavior in both mice and rats.

Olfactory mechanisms

Olfaction, the ability to perceive odors, is fundamental to all animal life on Earth. It allows species to detect food and to sense potential toxins in the environment, and it also assists in social interaction. There is growing appreciation for an association between the gut microbiota and the brain through olfaction across the animal kingdom, with species such as hyenas, birds, mongooses, and locusts using gut microbial by-products such as volatile fatty acids and esters to mediate communication (see below). Preliminary evidence suggests that both enteric and environmental bacteria can influence olfaction. For example, when the gut microbiota of *Drosophila melanogaster* was manipulated early in life to contain *Lactobacillus* species, the fruitflies displayed an increased olfactory-guided preference toward *Lactobacillus*-enriched medium. Similarly, *D. melanogaster* in which *Acetobacter* dominated the gut microbiota displayed a preference toward *Acetobacter*-enriched medium (*40*). Such results suggest that the composition of the microbiota can influence olfactory-directed behavior in some animals.

Perhaps the most striking observations regarding a role for the gut microbiota in olfaction have arisen in germ-free mice. The olfactory epithelium of germ-free mice displays a thinning of the layer of ciliated epithelium relative to control animals (*41*). Moreover, expression of genes linked to olfactory receptor transduction and xenobiotic metabolism were all found to be reduced in the absence of microbiota. These transcriptional changes in olfactory transduction and metabolism corresponded with alterations in olfactory detection, with a greater activation of olfactory sensory neurons of germ-free mice in response to various odorants (*41*). Given that mice rely on olfaction to facilitate social interaction, alterations to the olfactory system in the absence of a gastrointestinal microbiota may contribute toward the behavioral deficits observed in germ-free mice.

Microbiota and social behavior

Sociability varies markedly among animal taxa and associates with different lifestyle behaviors (*42*) (Table 1). Sociability can also vary over time and within species. For example, most bears (Ursidae) are largely nonsocial for the majority of their life but highly social during breeding season. Whether the gut microbiota influences this spectrum of sociability in bears, and indeed in most species, and how this might act alongside other causal factors (such as genetics, development, and environmental factors) (Fig. 3) in the wild, remains very poorly understood. Nonetheless, evidence suggests that selection pressures over the course of evolutionary history may have influenced an association between gut bacteria and social behavior. Although some studies suggest that the gut microbiota can influence social behavior, other evidence suggests that social behavior allows horizontal transmission of microbes between conspecifics (transfer of

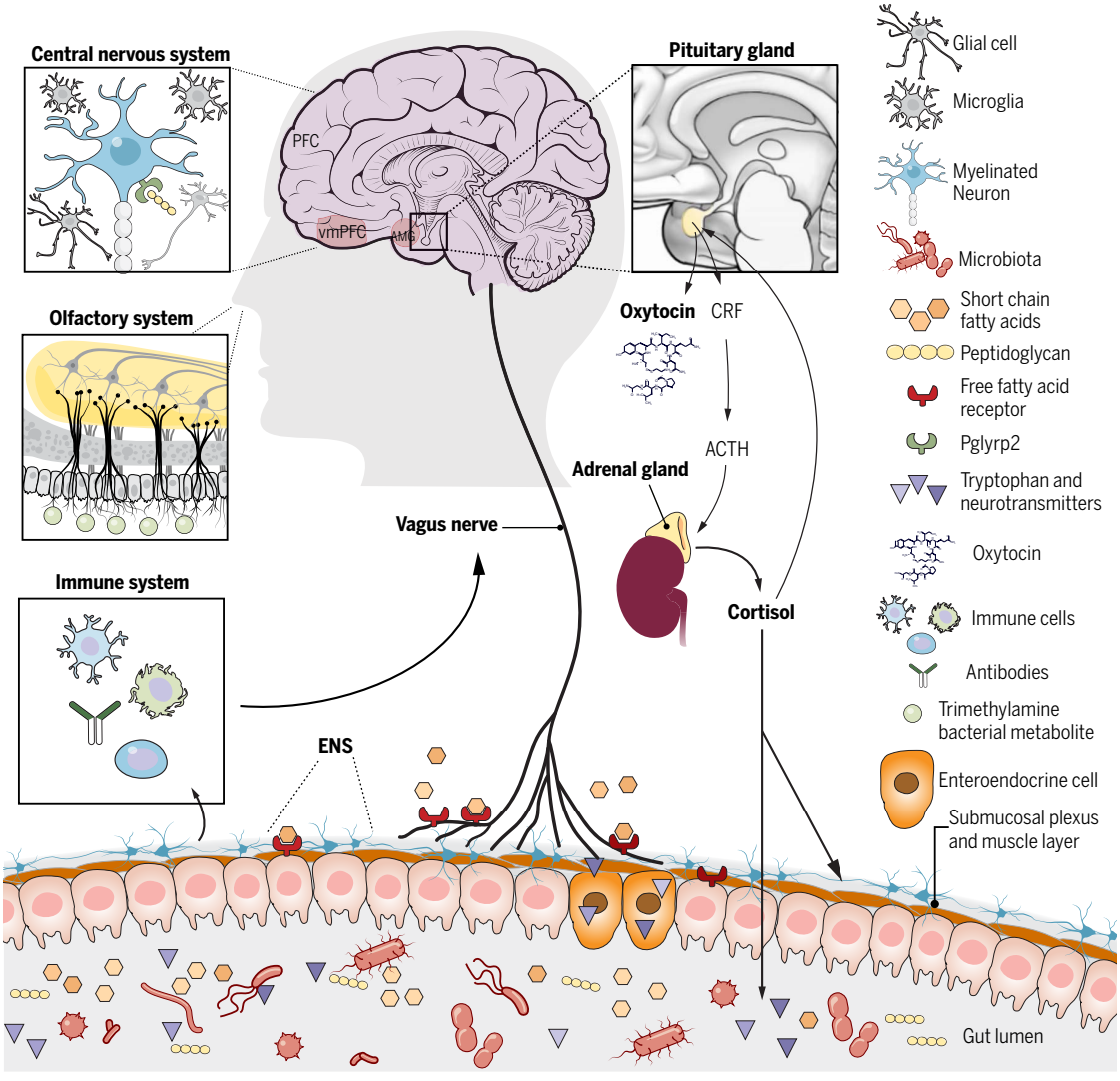


Fig. 2. Biological pathways underlying the regulation of social behavior by gut microbiota. There are numerous pathways through which the gut microbiota may influence behavioral processes such as sociability. Although additional unidentified metabolites and pathways connecting gut microbiota and the brain may exist, much focus has been on the bidirectional communication mediated via neural immune and metabolic routes. Bacterial fermentation and metabolism in the gastrointestinal tract lead to the production of metabolites such as neurotransmitters and short-chain fatty acids (SCFAs). SCFAs may be indirectly capable of influencing brain physiology and behavior through binding to and activating free fatty acid receptors (FFARs) expressed on the vagus nerve. Additionally, their ability to inhibit histone deacetylases locally within the gastrointestinal system may indirectly influence signaling of various mediators to the brain. Vagotomy studies have provided empirical evidence that the vagus nerve is an additional route through which the microbiota can communicate with the brain. The association between the gut microbiota and the immune system is another highly explored pathway through which commensal bacteria can exert their influence on brain physiology and behavior. Bacterial peptidoglycan expressed on the cell wall of Gram-negative and Gram-positive bacteria is capable of influencing the development of social behavior through the activation of specific pathogen recognition receptors, such as PGLYRP2, expressed in the brain (central nervous system inset). The microbiota can also influence social interaction through the excretion of metabolites that act as olfactory pheromones. Trimethylamine secreted in mouse urine can facilitate social cohesion of mouse conspecifics through the activation of olfactory receptors (olfactory system inset). Through these various pathways, the gut microbiota has been shown to modulate multiple central physiological processes such as neuroinflammation, serotonin turnover, myelination, and the secretion of the prosocial hormone oxytocin, thereby providing mechanistic insights into how gut bacteria influence social behavior. After exposure to a stressor, adrenocorticotropic hormone (ACTH) is released from the anterior pituitary gland (pituitary gland inset) and stimulates the release of stress hormone glucocorticoids (cortisol in humans, bears, ruminants, fish, and some rodents; corticosterone in rats, mice, birds, and reptiles). Glucocorticoids influence metabolism and mediate immune activation, among other systemwide effects. Exposure of commensal bacteria to glucocorticoids has been shown to decrease their relative abundance. Moreover, under conditions of chronic stress, increased release of glucocorticoids is associated with a reduction in gut microbiota diversity and richness.

microbiota across members of the same species that are not parent-child pairs), which may be evolutionarily beneficial for the microbiota. Thus, there appears to be a bidirectional relationship between the microbiota and social behaviors.

In addition to taking care when interpreting the direction of causality in correlational studies from the wild, caution is also advised when studying wild animals under captive conditions. Moving animals from the wild to captivity can cause substantial shifts in the composition of the gut microbiota in many animals, including bears (*43*), primates (*44*, *45*), horses (*46*), birds (*47*), and reptiles (*48*). This is to be expected, not just because the diets of wild animals are more diverse and can be difficult to acquire, but also because they are likely exposed to a more diverse environmental microbiota than captive animals. What this means for our ability to extrapolate findings from laboratory studies to animals in the wild, and especially to humans, remains to be clarified.

Sociability

Social interaction can influence the transmission of microbiota among conspecifics for many invertebrate species. For example, transmission of microbiota among termite (Blattodea) conspecifics can occur through social events such as coprophagia (consumption of feces) and proctodeal trophallaxis

Table 1. The relationship between microbiota and social behavior across the animal kingdom. Examining the microbiota composition of social and nonsocial species reveals that the same bacterial phyla are present in many animal species. However, different species use their associated microbiota in various ways to facilitate various forms of social interaction. For each animal, gut bacterial phyla are ranked in terms of the most to least abundant. For each study cited, the microbiota analysis was performed on fecal samples with the exception of the termite and honey bee studies, in which proctodeal segments were analyzed.

Species	Behavior	Ranking of dominant phyla in the microbiota	Relationship between social behavior and microbiota	Reference
Honey bee (*Apis mellifera*)	This eusocial invertebrate species exists within colonies consisting of a queen bee along with worker and soldier bees. Worker and soldier bees interact in a cooperative manner to ensure maintenance and survival of the colony.	1. Firmicutes 2. Actinobacteria 3. Proteobacteria	Social interaction facilitates horizontal transmission of microbiota that confers immune resistance against pathogens.	(*51*)
Desert locust (*Schistocerca gregaria*)	Desert locusts can shift from solitary to gregarious behavior depending on the environment and other factors. During the gregarious phase, locusts exist in large swarms, which aids in protecting them from predators.	Proteobacteria	Volatile fatty acids produced by the proteobacterium *Pantoea agglomerans* facilitate social cohesion of locust swarms.	(*66*, *140*)
Firebrat (*Thermobia domestica*)	Although they lack any known form of long-distance communication, firebrats gather around conspecific feces and former firebrat shelters. Moreover, these insects are capable of locating mates in their environment, presumably through odor detection.	1. Proteobacteria 2. Firmicutes	The bacterium *Enterobacter cloacae* present in the feces of firebrats mediates aggregation of conspecifics. The aggregation leads to the horizontal transmission of microbiota.	(*67*, *68*)
Termite (*Mastotermes darwiniensis*)	Termites are an eusocial insect species existing within a colony of multiple queens along with soldier and worker termites. Worker termites undertake the most work in the colony, cooperating in food storage as well as brood and nest maintenance.	1. Spirochaetes 2. Bacteroidetes 3. Firmicutes	Social interaction facilitates the horizontal transmission of microbiota that aids in food digestion.	(*62*, *63*)
Zebrafish (*Danio rerio*)	This species of fish aggregates into large groups, known as shoals. They can also exhibit aggression toward conspecifics, which typically arises as a result of territoriality. These fish can exhibit anxiety-like behavior when under threat from other animals.	1. Fusobacteria 2. Proteobacteria 3. Firmicutes	Modulation of the microbiota has been shown to influence shoaling behavior of zebrafish. Antibiotic treatment reduces shoaling behavior. Conversely, probiotic supplementation can increase shoaling behavior.	(*136*, *141*)
Zebra finch (*Taeniopygia guttata*)	The zebra finch is a social species that typically forms monogamous pair bonds during mating season. These birds tend to forage in groups for food rather than individually.	1. Firmicutes 2. Proteobacteria	Zebra finches have been shown to transmit bacteria through allogrooming that results in colonization of the gastrointestinal tract.	(*142*, *143*)

continued on next page

Species	Behavior	Ranking of dominant phyla in the microbiota	Relationship between social behavior and microbiota	Reference
Mouse (*Mus musculus*)	Rodents such as mice are social animals that prefer to exist within groups. Mice react aversely to social isolation, which is considered a stressor on the animal. Mice participate in cooperative behaviors such as grooming and play.	1. Firmicutes 2. Bacteroidetes 3. Proteobacteria 4. Actinobacteria	1. The microbial metabolite trimethylamine is excreted in the urine of mice and acts as a chemoattractant toward mouse conspecifics and a repellent of predators such as rats. 2. Mouse models of autism display microbiota alterations in addition to deficits in social behavior. 3. Germ-free and antibiotic-treated mice display deficits in social behavior that can be partly restored after reconstitution with microbiota.	(*15*, *17*, *109*, *130*, *134*)
Hyena (*Hyaena hyaena*)	Hyenas live in large social communities called clans. Females are typically the dominant sex in these communities and can dominate males and subordinate females. Social cognition is quite developed in hyenas, with animals capable of recognizing individual conspecifics and even distant relatives.	1. Firmicutes 2. Actinobacteria 3. Bacteroidetes 4. Fusobacteria	Fermentative bacteria in the scent glands produce volatile fatty acids that facilitate specific odors for social recognition among hyena conspecifics.	(*14*)
Meerkats (*Suricata suricatta*)	Meerkats are social animals existing within groups of up to 30 conspecifics. They engage in cooperative behaviors such as grooming and teaching of young to forage for food; females protect offspring of the dominant members of the group.	1. Firmicutes 2. Bacteroidetes 3. Proteobacteria 4. Actinobacteria 5. Fusobacteria	The anal gland of the meerkat contains volatile chemicals that correlate with the presence of various bacterial species. Genes related to lipid metabolism are expressed at higher amounts in the anal pouch of dominant males compared to subordinates, which may enhance communication.	(*71*)
Koala (*Phascolarctos cinereus*)	Koalas are typically asocial, with females and males existing in separate territories until breeding season. Although koalas tend to avoid aggressive interactions, antagonistic behaviors can occur, especially when one male occupies the territory of another male.	1. Bacteroidetes 2. Firmicutes	At weaning, the mother produces a liquid form of feces, called pap, which the offspring (joey) ingests. This pap contains a microbiota that aids in the digestion of eucalyptus, the primary food of the koala.	(*144*)
Gorilla (*Gorilla gorilla*)	This great ape species exists within communities typically comprising an alpha male, several females, and offspring. Multiple-male troops also exist. Gorillas engage in social behaviors such as grooming and playing.	1. Firmicutes 2. Proteobacteria 3. Bacteroidetes	Less social gorillas have a reduced risk of contracting the Ebola-Zaire virus. The composition of the gorilla gut microbiota can be influenced by interactions with gorilla conspecifics and sympatry with other ape species.	(*61*, *145*)

continued on next page

Species	Behavior	Ranking of dominant phyla in the microbiota	Relationship between social behavior and microbiota	Reference
Chimpanzee (*Pan troglodytes*)	Primates exhibit highly social behavior within large communities. Chimpanzees participate in cooperative behaviors such as grooming and play.	1. Proteobacteria 2. Firmicutes 3. Bacteroidetes	Social interaction among conspecifics results in the horizontal transmission of microbiota, resulting in the preservation of microbial diversity across generations.	(*61*, *146*)
Humans (*Homo sapiens*)	Humans are highly social animals existing within large and complex social communities. Social interaction in humans consists of a wide variety of intricate languages, values, rituals, and cultures. Humans interact on a daily basis to facilitate work, education, and rearing of offspring.	1. Firmicutes 2. Bacteroidetes 3. Actinobacteria 4. Proteobacteria	1. Humans occupying the same environment share similar gut microbiota characteristics relative to those who do not. 2. Kissing can facilitate the horizontal transmission of microbiota from one individual to another. 3. Alterations to the composition of the gut microbiota have been documented in individuals with deficits in sociability such as autism spectrum disorder.	(*53*, *100*, *147*)

(transfer of food, fluid, or nutrients from the rectum of one animal to the mouth of another) (*49*). Similarly, honey bees (*Apis mellifera*) acquire gut microbiota after adult emergence from the pupa via social interaction with worker bees (*50*). Social interaction also facilitated the acquisition of a homogeneous gut microbiota phylotype among various species of honey bees, in contrast to solitary bees that harbor a more diverse microbiota containing bacteria associated with the environment as well as potentially pathogenic genera (such as *Wolbachia*) (*51*). The presence of bacterial genera such as *Bifidobacterium* and *Lactobacillus* in the gut microbiota of social bees can promote the production of SCFAs, which may serve important biological roles in nutritional provision during periods when food is scarce (*51*). Indeed, supplementation of honey bees with a combination of *Bifidobacterium* and *Lactobacillus* increased eusocial cooperative behaviors observed as enhanced hive work output (*52*).

Most studies of invertebrate and vertebrate microbiota to date have used low-resolution 16*S* DNA sequencing. Therefore, it is premature to identify any association between microbiota composition in an animal and its social proclivities at a strain or functional level. In the future, higher sequencing resolution and functional output provided by a shotgun metagenomic approach may allow the field to address such associations in greater detail by identifying bacterial strains and their predicted metabolic by-products influenced by social interactions.

Social interaction can shape the microbiota of many primate species via the horizontal transfer of bacteria. For instance, kissing in humans (*Homo sapiens*) facilitates the transfer of oral microbiota (*53*). Indeed, married couples have greater gut microbial diversity and species richness than individuals living alone, which may aid in understanding the health benefits of marriage compared to solitary living (*54*, *55*). Long-term cohabitation results in the convergence of human gut microbiota that is evident even at a strain level. However, the directionality and routes of transmission of microbiota are largely unknown because of the difficulty in providing evidence for such factors in a species with complex social intricacies (*55*). Intriguingly, female humans exhibit increased microbiome similarity with members of their households and spouses compared with males who live in the same household, which suggests that sex may be an important determinant in the transmission of gut microbiota in humans (*55*).

In primates, the weaning of infant rhesus monkeys (*Macaca mulatta*) into social groups leads to a convergence of gut microbial community structure, with changes observed in *Prevotella*, *Blautia*, and *Ruminococcus* taxa (*56*). Among baboon (*Simia hamadryas*) conspecifics, social behaviors such as grooming result in the convergence of core gut microbial taxa (*57*). Moreover, it appears that position within a social network, and not just social behavior itself, is an important correlate in shared gut microbial composition for some species, such as the red-bellied lemur (*Eulemur rubriventer*) (*58*). In a separate study on lemurs, the density of grooming networks was shown to correlate with microbiota homogeneity, with more gregarious members of a social group harboring a more diverse microbiota presumably through increased grooming behavior and scent marking (*59*). Social interaction may also influence gut bacterial diversity and species richness within and across generations of chimpanzees (*60*).

Although sociability can lead to microbiota transmission between animals of the same species, some evidence suggests that transmission between different species can also occur. For example, primate species in the same geographic area share more similar gut microbiota than the same species living in geographic isolation. This highlights the potential impact of the environment on horizontal microbial transmission and differentiation of gut microbiota between species (*61*). Consequently, social interaction may enable the preservation of gut microbial diversity across large periods of time, which may have important implications for the evolution and ecology of a particular species' microbiota.

Although variation in gut microbiota seems to covary with sociability across some species, this is not always the case. For example, both honey bees and termites are colonial and highly social, but they have markedly different microbiotas. Honey bees harbor a rather simple microbiota consisting of six to nine bacterial phylotypes, with *Bifidobacterium* (Actinobacteria) and *Lactobacillus* (Firmicutes) as the predominant genera (*49*, *51*). By contrast, the termite microbiota consists of hundreds of bacterial species, predominantly characterized by the Spirochaetes phylum, with the Firmicutes and Bacteroidetes phyla also present (*62*, *63*). Indeed, many of the bacterial species identified in the gut microbiota of the termite are endemic to the host species, with diet likely to be

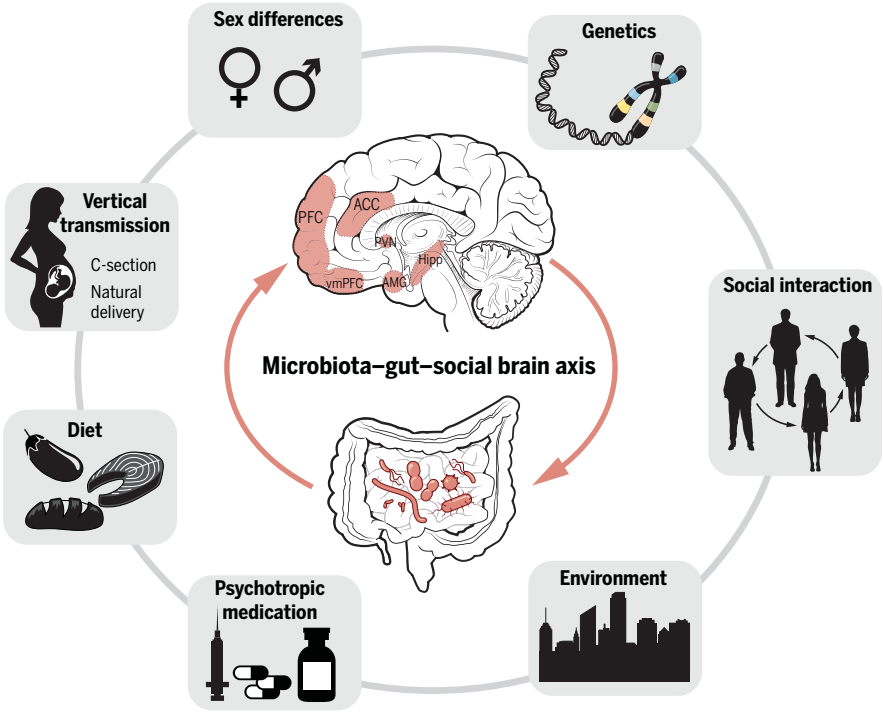


Fig. 3. The social brain is influenced by multiple biological and environmental factors. Social behavior is governed by multiple interconnected brain regions such as the hypothalamus, amygdala, cingulate cortex, and prefrontal cortex that are influenced by multiple extrinsic and intrinsic factors such as sex, genetic and epigenetic mechanisms, and the environment. Each of these factors may influence social behavior directly. However, they may also act in combination with one another to shape such behaviors. For instance, host genetics can influence the composition of the host gastrointestinal microbiota, thereby influencing the relative contribution of enteric bacteria toward social behavior. Moreover, extrinsic factors such as diet, psychotropic medication and environment can also affect the composition of the microbiota to indirectly modify behavior (*17*, *116*, *132*, *139*, *148*, *149*). PFC, prefrontal cortex; vmPFC, ventromedial prefrontal cortex; ACC, anterior cingulate cortex; AMG, amygdala; PVN, paraventricular nucleus of the hypothalamus.

an influential factor in shaping differences in microbiota composition (*62*, *64*, *65*). Thus, divergent evolutionary processes caused by distinct selective pressures could be at play, pointing to the need for considering phylogenetic influences when searching for microbial signatures of sociability.

Communication

For some invertebrate species, the gut microbiota can facilitate communication between conspecifics. In the gut of the desert locust (*Schistocerca gregaria*), the bacterium *Pantoea agglomerans* is responsible for the production of guaiacol, a volatile organic compound that serves as one of the main constituents in the locust swarming pheromone (*66*). Firebrats (*Thermobia domestica*; wingless hexapod insects) are known to aggregate with conspecifics in response to the presence of the bacterium *Enterobacter cloacae* found in their feces (*67*). Moreover, the aggregation of firebrats by this species of *Enterobacter* facilitates the horizontal transmission of this symbiont among conspecifics, thereby ensuring its survival and propagation in the host population (*68*). Volatile carboxylic acids produced by the gut microbiota of the cockroach species *Blattella germanica* mediate the aggregation of conspecifics (*69*). This was demonstrated through the inoculation of germ-free cockroaches with a cocktail of commensal bacterial species (*Enterococcus avium*, *Weissella cibaria*, *Pseudomonas japonica*, *Pseudomonas monteilii*, *Acinetobacter pittii*, *Acinetobacter* sp.), which resulted in the attraction of nymphs to their feces (*69*). The roles of the microbiota in mediating social communication in invertebrates is not limited to enteric bacteria; for example, certain gut fungi species in the bark beetle *Dendroctonus ponderosae* can also produce cohesion pheromones (*70*).

The microbiota may also assist in facilitating communication for some vertebrate species. For example, the microbial metabolite trimethylamine, a waste by-product of dietary choline metabolism by gut commensal bacteria, is expelled in the urine of numerous species. Remarkably, trimethylamine excreted in the urine of laboratory-raised male mice acts as a chemoattractant for other conspecifics (*15*). Moreover, the bacterial metabolite acts as a chemorepellent to rats, which are a natural predator to mice (*15*). Knockdown of TAAR5 (trace amine associated receptor 5) in mice abolished the prosocial properties of trimethylamine, thereby supporting a causal link between the gut microbiota and social interaction.

There is also emerging evidence of this phenomenon occurring in wild animals, although the inability to control for various confounding variables makes causality difficult to ascertain. For example, hyenas (from the family Hyaenidae) produce a paste from their scent glands that contains fermentative bacteria such as *Clostridium*, which synthesize volatile fatty acids (*14*). The strong odor associated with these volatile fatty acids supports the premise that hyena paste is used as a marker of territory or even social cohesion (*14*). Interestingly, comparisons between the volatile fatty acid profiles from the spotted hyena (*Crocuta crocuta*) and striped hyena (*Hyaena hyaena*) reveals marked differences, with a greater degree of variation in the highly social spotted hyena's paste compared to that of the less social striped hyena (*14*). Thus, the more diverse microbial-produced fatty acid profile produced by the spotted hyena may facilitate more complex interactions. Similar to the observations in hyenas, the anal pouch of wild meerkats (*Suricata suricatta*) contains bacterial genera such as *Corynebacterium*, *Anaerococcus*, and *Porphyromonas* (*71*). Bacterial genes encoding for lipid biogenesis were more prevalent in the anal pouch of dominant males compared with females and subordinates (*71*), pointing to the possibility that volatile lipids of microbial origin play a role in the olfactory communication of status within meerkat groups.

The microbiota of some species may function in the discrimination of conspecifics. For example, the uropygial gland of birds, which functions primarily to provide an oily substance for waterproofing feathers, is also considered to be the main odor source in this taxa; this oil harbors a unique microbiota containing fermentative bacteria that produce a wide array of volatile fatty acids, hydrocarbons, and esters (*47*, *72*). Although for a long time it was thought that most species of birds rely primarily on vocal communication, smell is increasingly realized to play a role. The mixture of volatile fatty acids and other chemicals allows birds such as starlings (*Sturnus unicolor*) to discriminate between the sexes. In addition, horses (*Equus ferus caballus*) are capable of distinguishing between conspecifics according to the smell of their feces, which is microbial in origin (*46*). Moreover, the anal gland of the Indian mongoose (*Herpestes auropunctatus*) produces volatile chemicals as a by-product of bacterial metabolism that facilitates conspecific recognition (*73*). Consequently, the microbiota may be an important mechanism of social recognition for many animals.

Table 2. Clinical and preclinical studies of microbiota-based interventions for the treatment of social behavior deficits. ASD, autism spectrum disorder; ATEC, Autism Treatment Evaluation Checklist; CFU, colony-forming units; PBS, phosphate-buffered saline; FOS, fructo-oligosaccharide; GABA, γ-aminobutyric acid; GOS, galacto-oligosaccharide; poly(I:C), polyinosinic:polycytidylic acid; Shank3, SH3 and multiple ankyrin repeat domains 3.

Subjects	Intervention	Behavioral outcomes	Biological outcomes	Reference
Clinical studies				
17 ASD subjects (4 to 16 years of age)	Daily oral *Lactobacillus plantarum* WCFS1 (4×10^{10} CFU per capsule) administration for 12 weeks	Anxiety and antisocial measures improved after probiotic supplementation, as assessed by the standardized developmental behavioral checklist	Increased relative abundance of *Lactobacillus* species and a decrease in *Clostridium* cluster XIVa in fecal samples	(*113*)
30 ASD subjects (19 boys and 11 girls; 5 to 9 years of age); 30 age- and gender-matched controls from ASD participants' families	Daily oral *L. rhamnosus*, *L. acidophilus*, and *Bifidobacterium longum* (500×10^6 CFU per sachet) for 3 months	Sociability, speech and language communication, and sensory awareness improved after treatment, as assessed by the ATEC checklist	Probiotic treatment improved gastrointestinal symptoms (abdominal pain, flatulence, constipation, etc.)	(*114*)
18 ASD subjects (7 to 17 years of age); 20 age- and gender-matched neurotypical controls	Oral dose of standard human microbiota cocktail (2.5×10^{12} CFU for 2 days followed by 2.5×10^9 CFU maintenance dose for 8 weeks)	Sociability, communication, and hyperactivity scores improved after treatment, as assessed by the Childhood Autism Rating Scale and Parent Global Impressions III scale	Gastrointestinal symptoms (i.e., constipation, abdominal pain, etc.) improved by 80% according to the Gastrointestinal Symptom Rating Scale	(*115*)
26 ASD subjects (4 to 11 years of age)	Oral dose of 1.8 g of Bimuno-GOS (B-GOS) or maltodextrin for 6 weeks combined with a gluten and casein exclusion diet	Antisocial behavior improved after treatment, as assessed by the ATEC checklist and the Autism Spectrum Quotient	Exclusionary diet improved gastrointestinal symptoms (i.e., abdominal pain); B-GOS consumption increased the relative abundance of *B. longum* in fecal samples and reduced urinary arachidonic acid	(*128*)
13 male ASD subjects (10 to 12 years of age)	Oral dose of 1.5 g of omega-3 fatty acids (eicosapentanoic acid and docosahexanoic acid) per day for 6 weeks	Hyperactive behavior improved after treatment, as assessed by the Aberrant Behavior Checklist	No measurements included in study	(*124*)
24 ASD subjects (3 to 8 years of age)	Oral dose of 1.3 g of omega-3 fatty acids (eicosapentanoic acid and docosahexanoic acid) for 12 weeks	Nonsignificant improvement in hyperactive behavior, as assessed by the Aberrant Behavior Checklist	Decreases in percentages of monosaturated and omega-9 fatty acids in blood plasma after treatment	(*125*)
Preclinical studies				
Male C57BL/6N mice from mothers administered either saline vehicle or poly(I:C) 20 mg/kg (induces in utero inflammation; environmental model of ASD) via the intraperitoneal cavity on gestational day 12.5; aged 6 weeks at the beginning of behavioral testing	1×10^{10} CFU of *Bacteroides fragilis* NCTC 9343 or vehicle was administered in sugar-free applesauce over standard rodent chow	Improvement in anxiety-like and stereotyped behaviors after probiotic treatment; treatment also improved ultrasonic vocalizations; sociability was unaffected by treatment	Treatment with *B. fragilis* ameliorated heightened intestinal permeability, intestinal inflammation, and alterations to the intestinal microbiota	(*109*)
Male C57BL6/J mice from mothers fed a high-fat diet (60% fat consistency; environmental model of ASD) before and during pregnancy until weaning of offspring were used for experimentation; mice were aged 7 to 12 weeks at the beginning of behavioral testing	1×10^8 CFU of *L. reuteri* MM4-1A or a PBS vehicle was administered in drinking water and changed daily	Treatment with *L. reuteri* improved deficits in social behavior; anxiety or stereotyped behaviors were unaffected by treatment	Treatment with *L. reuteri* increased hypothalamic oxytocin expression	(*17*)

continued on next page

Subjects	Intervention	Behavioral outcomes	Biological outcomes	Reference
Male C57BL/6J mice aged 7 weeks at the beginning of behavioral testing	FOS and GOS were administered separately or in combination in drinking water at a dose of 0.3 to 0.4 g per mouse per day	A combination of GOS and FOS reversed chronic social stress–induced deficits in social interaction, anxiety, and cognition	A combination of GOS and FOS protected gut microbiota composition against exposure to chronic stress; the combination of both prebiotics reduced circulating corticosterone and attenuated stress-induced pro-inflammatory cytokine production	(*88*)
Male and female *Shank3* (ASD risk gene; genetic model of ASD) knockout and wild-type mice aged 8 to 11 weeks at the beginning of behavioral testing	1×10^9 CFU of *L. reuteri* MM4-1A or a PBS vehicle was administered via oral gavage twice a week for 3 weeks	Treatment with *L. reuteri* improved deficits in social behavior in male but not female *Shank3* knockout mice; *L. reuteri* also reduced stereotyped behaviors	Treatment with *L. reuteri* increased the expression of $GABA_A$ receptor subunits in the prefrontal cortex and hippocampus in both male and female Shank3 mice; oxytocin expression in the hypothalamus was also increased after treatment	(*107*)
Male *Shank3* knockout (genetic model of ASD), oxytocin receptor knockout, germ-free, BTBR, and C57BL/6J mice exposed to in utero valproic acid (teratogenic drug; environmental model of ASD) on gestational day 12.5	1×10^8 CFU of *L. reuteri* MM4-1A or a PBS vehicle was administered in drinking water and changed daily	Treatment with *L. reuteri* improved deficits in social behavior in all animal models of ASD tested	Treatment with *L. reuteri* increased hypothalamic expression of oxytocin in all animal models tested	(*108*)

Social immunity

Group living offers a wide range of potential benefits, but it also comes with many costs, including increased exposure to infectious agents. Social gorillas, for example, are thought to be more susceptible to acquiring the Ebola-Zaire virus than solitary ones (*74*). Moreover, blood parasite levels increase with sociability among bird species (*75*). This increased threat of exposure to infectious agents with sociability is counterbalanced by increased microbiota diversity (*18*, *54*). This allows the immune system to function in cooperation with the microbiota to protect against harmful microorganisms (*76*, *77*). Immunity and host response to invading pathogens may also have an impact on the microbial underpinnings of social behavior, given that the immune system serves as a conduit between enteric commensal bacteria and the CNS through a variety of immune signaling mechanisms [reviewed in (*78*)]. For example, many species of birds invest considerable periods of time in cooperative maintenance behaviors, such as allogrooming (social grooming between members of the same species) (*79*), thus increasing the endoparasitic load within the gastrointestinal system (*80*). Intriguingly, colonization of the gut of some species of animals with helminths (parasitic worms) can confer increased microbial diversity while also beneficially modulating host immunity through their anti-inflammatory properties (*81*, *82*). In such instances, social behaviors (e.g., allogrooming) may be beneficial to the host and the intestinal microbiota because they improve microbial diversity and prevent the growth of pathogenic bacteria, potentially leading to improved overall fitness.

Similar to that observed in vertebrates, the host immune response of some invertebrates also appears to be an important selection pressure in promoting social behavior. For example, the acquisition of microbiota through social interaction is vital in protecting bumble bees (*Bombus terrestris*) against the highly virulent parasite *Crithidia bombi* (*83*). Moreover, antimicrobial compounds produced by eusocial bees (those that live in colonies), such as *Trigona carbonaria*, are orders of magnitude more effective than those produced by the asocial bee species *Amegilla asserta* (*84*). As bee colony size increases, so does genetic relatedness and antimicrobial strength among eusocial species. With increases in group sizes and genetic relatedness, increased prevalence and susceptibility to microbial pathogens likely acted as a selection pressure to drive the evolution of stronger antimicrobial activity in bees (*84*). Additionally, social immunity among ant species is an important defensive behavior that ensures the survival of individual members within the insect society. Garden ants (*Lasius neglectus*) have been shown to selectively groom broods that were infected with the fungus *Metarhizium brunneum* while also producing a formic acid–based chemical disinfectant that inhibits the growth of fungal spores on the broods (*85*). A carbohydrate-rich diet increased social immunity among garden ants while also reducing worker ant mortality rates when the colony was infected with *Metarhizium*, indicating that modulation of microbiota through diet can further improve this behavior (*86*).

Diet and stress

The positive effects of sociability on animal behavior are typically accompanied by a wide range of negative effects, including stress. Stress is an evolutionary adaption to protect animals in danger by mediating a fight-or-flight response. In the short term, stress responses are beneficial because they aid the survival of the animal. However, long-term exposure to stress can be detrimental to both physiological and behavioral health. The perception of stress is instigated not only in response to dangers in the environment but also after certain social interactions. By elevating glucocorticoid hormones, social stress can even affect the gut microbiota, observed as a reduction in the diversity of enteric bacteria, in addition to the many other physiological effects of stress (*87*, *88*). In the North American barn swallow (*Hirundo rustica erythrogaster*), for example, increased social interaction between the sexes during the mating season is associated with higher corticosterone levels and reduced gut microbial diversity (*89*). Moreover,

chronic exposure to social stress in mice also leads to a reduction in gut microbiota diversity (*88*). With decreases in the availability of salmon, densities of the normally asocial black bear (*Ursus americanus*) increase, which correlates with an elevation in circulating cortisol. An increase in social stress among black bears is likely to have deleterious effects on their microbiota through a reduction in nutritional intake, thereby affecting gut microbial diversity. Social stress–induced reductions in nutritional intake may have detrimental effects on bears during hibernation periods, for which the microbiota plays an important role in regulating lipid, bile acid, and glucose metabolism (*90*).

Social stress can lead to a decline in health and fertility and increase susceptibility to disease, thereby compromising the overall fitness of a species (*91*). In the case of carnivorous animals such as bears, solitary behavior may be beneficial to the gut microbiota because it promotes sufficient nutritional intake while minimizing cortisol levels, which has been shown to reduce gut bacterial diversity in other species (*88*). Although social interactions may be harmful to the gut microbiota through increased exposure to stress, they can also be beneficial. The balance between the beneficial and detrimental effects of social interaction on the gut microbiota appears to be largely relationship-dependent. However, environmental factors (i.e., availability of food) may also play a critical role.

Herbivorous or carnivorous diets and their subsequent effect on the composition of the gut microbiota may also have influenced the evolution of social behaviors in some species. In herbivores, the presence of microbes is vital for the digestion of plant-derived dietary components such as cellulose and hemicellulose (*92*). Such a diverse diet could have hypothetically driven the evolution of social interactions to facilitate the horizontal transfer of specialized microbiota among conspecifics to aid digestion (*92*, *93*). Although such a hypothesis may be difficult to assess in higher animals such as mammals, and is probably modest given the importance of other better-known selection pressures (such as predation, immune response to pathogens, or sexual competition), there is some evidence in invertebrate species to suggest that diet may have facilitated the acquisition of social behavior.

The cockroach (*Periplaneta americana*) harbors intracellular symbionts in addition to a gut microbial community, whereas the closely related but more social termite species contains only gastrointestinal microbiota (*94*). One particular nongastrointestinal bacterial symbiont, *Blattabacterium*, serves an important role in nutrient provision for the cockroach by synthesizing vitamins and amino acids through nitrogen fixation (*95*). Interestingly, this species of bacteria is either completely absent or has undergone genome shrinkage in termites (*94*), the functional loss of which is thought to be compensated for by having a diverse hindgut microbiota facilitated by the evolution of social behavior and greater transmission of microbiota among conspecifics (*95*). In support of this idea, the absence of *Blattabacterium* may have led to the evolution of social behaviors in termites to facilitate the reliable transmission of microbiota among conspecifics to enable the digestion of a complex lignocellulose diet (*95*). In support of this idea, limited transmission of microbiota has been observed among cockroach conspecifics, which harbor a gut microbiota community dominated by *Bacteroides*, *Paludibacter*, and *Parabacteroides* species (*49*, *95*). Conversely, the microbiota of the more social *Mastotermes darwiniensis* and *Heterotermes aureus* termite species is characterized by a high degree of homogeneity among conspecifics, suggesting horizontal transmission, with bacterial genera including *Tannerella*, *Clostridium*, *Treponema*, and Rikenellaceae being most abundant (*49*, *95*). Consequently, in some instances, selection of a social phenotype may allow for the preservation of certain host-environmental interactions (i.e., nutrient provision via microbiota) not only across conspecifics but across generations.

Social disorders

Given the complex, sometimes bidirectional effects of the microbiota and the social brain across the animal kingdom, it is perhaps not surprising that evidence for an important role of the microbiota in disorders of sociability in humans is accumulating. Deficits in social behavior manifest in several neuropsychiatric conditions such as ASDs, schizophrenia, social anxiety, and depression, with patients either incapable of interacting with others or withdrawing from social interaction (*8*). Because social interaction can be such a vital component of human mental health, altered behavior may have deleterious effects on overall fitness and mortality (*96*). Interestingly, several preclinical and clinical studies documented perturbations in the gastrointestinal microbiota (including reductions in bacterial diversity and reduced abundance of beneficial bacteria) among individuals with these neuropsychiatric disorders, and dysregulation may be linked with the behavioral symptoms observed (*17*, *88*, *97*–*99*). Analysis of the fecal microbiota of children with ASDs, for example, reveals profound alterations in microbial diversity, with losses in key bacterial taxa (such as *Bifidobacterium*) along with the presence of harmful strains within genera frequently associated with pathology, such as *Clostridium* and *Desulfovibrio* (*100*–*102*).

Clostridium perfringens strains isolated from the microbiota of children with ASDs were found to express the gene encoding β2 toxin, *cpb2*, to a greater extent than the same strain isolated from the microbiota of neurotypical children (*102*). This toxin is associated with various gastrointestinal diseases, which may help to explain the comorbid gastrointestinal symptoms (such as bloating, constipation, acid reflux, and diarrhea) that are frequently observed in ASD individuals. However, the etiology of this perturbed microbiota in ASDs is currently unknown and most likely reflects several biological, genetic, and environmental factors (*100*, *103*). For example, the mode of childbirth (vaginally or Caesarean section) and its influence on the vertical transmission of microbiota from mother to offspring may affect neurodevelopment. However, epidemiology studies vary, with some studies showing a modest relationship between mode of delivery and incidence of ASDs, psychosis, and attention deficit–hyperactivity disorder (ADHD) and others finding no relationship. In a study of ~2.7 million individuals, birth via Caesarean section was associated with a modest ~20% increase in the relative risk of an ASD diagnosis. However, this effect was not evident when a sub-analysis of sibling controls was added, implying that underlying familial factors such as genetics may be contributing (*104*). Nonetheless, more work is needed to understand whether there are long-term consequences of early-life microbiota disturbances for the social brain.

Diet confounds the interpretation of microbiota data from children with ASDs because many of them exhibit a stereotyped (persistent, repetitive, and inflexible) behavior pattern in their dietary intake and may avoid certain food types that benefit the microbiota. For example, prebiotics, such as inulin-rich foods, are indigestible dietary components metabolized by the gut microbiota that promote the growth of beneficial bacteria including the genera *Bifidobacterium* and *Lactobacillus*. Indeed, one clinical study observed that a large increase in the abundance of the genus *Cyanobacterium* in the fecal microbiota of several children with ASDs was anecdotally predicted by their dietary intake of chia seeds (*100*). Thus, the reported alterations to the composition of the microbiota of autistic individuals may simply be due to the absence of sufficient nutrient intake. Moreover, some psychotropic medications (such as the antipsychotic drug olanzapine) can negatively alter the microbiota composition, which represents an additional consideration when investigating links to microbiota in certain psychiatric conditions (*105*). Consequently, there is variable evidence of alterations to the microbiota in individuals with ASDs, with no consistent microbial signature that is representative of the

neurodevelopmental disorder. Despite this limitation, the clinical findings currently demonstrate that the microbiota is affected in conditions such as ASDs, and future studies with more patients (for statistical power) and appropriate controls may provide greater insights into any causative role for gut microbiota in such disorders.

Targeting the microbiota

Associations between microbiota and social disorders suggest that targeting the microbiota could ameliorate deficits in social behavior. Microbiota-based strategies have demonstrated the potential to alter social behavior in various preclinical models, with some preliminary evidence suggesting effects in humans (Table 2). Such strategies may have broad implications not only for the treatment of social brain disorders in humans, but also for the rest of the animal kingdom in terms of potentially reducing stress while in captivity, aiding in mating programs, and enhancing survival in the wild.

Probiotics

Although perturbations to the microbiota often negatively influence social behavior, modulation of gut bacteria through probiotic administration can have a beneficial effect. For example, mice derived from mothers on a high-fat diet have an altered microbiota composition (with notable reductions in several *Lactobacillus* species) and display a reduced ability to discriminate between a conspecific and an empty chamber, as well as a reduced ability to discriminate between a familiar and an unknown conspecific. These social deficits can be reversed after treatment with *Lactobacillus reuteri* (*17*), an effect that is linked to increased CNS expression of the prosocial hormone oxytocin, in the paraventricular nucleus of the hypothalamus and its secretion into blood circulation (*17*, *106*). Adult administration of *Lactobacillus reuteri* has been shown to improve social behavioral deficits in an oxytocin-dependent manner in multiple animal models of ASD [including in utero valproic acid exposure, the BTBR mouse model of ASD, oxytocin receptor knockout mouse, and genetic knockdown of the autism candidate gene *Shank3* (SH3 and multiple ankyrin repeat domains 3) in mice], further validating its preclinical efficacy and potential mechanism of action (*17*, *107*, *108*).

Other bacterial strains, such as *Bacteroides fragilis*, have efficacy in improving certain ASD-associated behaviors in the maternal immune activation mouse model of ASD (*109*). Interestingly, *Bacteroides fragilis* had little impact on social recognition or social cognitive processes in mice, demonstrating that the impact of microbiota on specific social behaviors may be strain-specific. Although *Bacteroides fragilis* is a commensal gut bacterium and influences human health through modulation of host immune responses and gastrointestinal development (from infancy to adulthood), it is also an opportunistic pathogen and is associated with an increased risk for gastrointestinal cancer and inflammatory bowel disease (*110*, *111*). Consequently, despite its efficacy in improving ASD-associated behavior in mice, the status of *Bacteroides fragilis* as a probiotic is hindered by its potential pathogenic effects.

Taken together, these preclinical observations must be interpreted with caution. *Lactobacillus* species have previously been effective in improving behavior preclinically in mice while having no observable effect when tested in healthy humans (*25*, *112*), possibly because the microbiota of a mouse differs considerably from that of a human. Consequently, the efficacy of probiotics to modify behavior established in preclinical studies of mice may not always align with clinical observations. Moreover, although there has been considerable development in assessing the efficacy of probiotics to ameliorate ASD-related behavior in preclinical models, clinical data are currently limited. In a small double-blind, randomized, placebo-controlled trial, the probiotic *Lactobacillus plantarum* WCSF1 was found to improve antisocial and anxiety behavior in children with ASDs, as assessed by parental rating of the standardized developmental behavioral checklist (*113*). However, the dropout rates from this study were quite high, which likely affected the statistical power of the results (*113*). In an open-label study, ASD behavior, as assessed by the autism treatment evaluation checklist, was improved in 30 children with ASDs after treatment with a probiotic cocktail comprising *Bifidobacterium longum*, *Lactobacillus acidophilus*, and *Lactobacillus rhamnosus* for 3 months (*114*). In a separate open-label study, children with ASDs treated with a standardized human microbiota cocktail displayed improvement in some of the associated behavioral and gastrointestinal symptoms (*115*). Although these clinical observations are promising, they must be interpreted with caution, especially considering that open-label investigations have a high risk of both selection and performance bias.

Diet and prebiotics

Dietary composition may also influence social behaviors through modulating the gut microbiota (*116*). Diets rich in sources of omega-3 polyunsaturated fatty acids (e.g., certain species of fish, walnuts, and soybeans) beneficially modulated gut microbial composition by increasing the relative abundance of beneficial bacteria such as *Bifidobacterium* and *Lactobacillus* species while also improving social interaction in rats, mice, and guinea pigs (*Cavia porcellus*) (*117*–*120*). Conversely, early-life dietary deficiency of omega-3 fatty acids led to deficits in social recognition in mice, highlighting the importance of diet in facilitating normal brain neurodevelopment and behavior (*120*). The mechanism by which omega-3 fatty acids modulate social behaviors has not been fully elucidated, and the relative contribution of their effects on microbiota versus host cellular oxidative stress and inflammation remain unclear (*121*–*123*). Moreover, it is unknown whether any of the potential beneficial effects of omega-3 fatty acids reported in small open-label clinical trials are due to their effects on the microbiota (*124*, *125*).

Diets can affect other aspects of social behavior. For example, a diet rich in fat and low in carbohydrates decreased aggression and promoted non-agonistic interactions in pigs (from the family *Suidae*) and nonhuman primates (*126*, *127*). Prebiotics also promote social behavior in some instances. The prebiotics galacto-oligosaccharide (GOS) and fructo-oligosaccharide (FOS) increased social interaction in chronically stressed mice, which was associated with alterations in gut microbiota composition and metabolite production (*88*). Specifically, ingestion of a FOS and GOS combination increased the relative abundance of the key bacterial genera *Akkermansia* and *Bacteroides* while also reducing the presence of potentially pathogenic genera such as *Desulfovibrio* (*88*). These changes were also associated with alterations in microbial metabolism, with increased cecal concentrations of acetate and propionate, a concomitant reduction in butyrate levels, and a reduction in circulating tryptophan concentrations (*88*). More recently, a combination of a gluten- and casein-free diet with the prebiotic Bimuno-GOS (B-GOS) resulted in an improvement in gastrointestinal and social behavior symptoms in a pilot study of children with ASDs, which was associated with an increase in the abundance of *Bifidobacterium longum* in fecal samples (*128*). However, the study did not investigate whether the increase in the abundance of this strain had any bearing on the behavioral changes observed. Although these small-scale clinical studies are certainly promising, interpreting their clinical importance is limited by their small sample size and experimental design. Appropriate statistically powered and double-blinded clinical studies are required to fully elucidate the clinical efficacy of any potential intervention for treating disorders of the social brain.

Conclusions and future perspectives

Many theories have been proposed to account for how behaviors such as sociability evolved and why animals exhibit these behaviors along a spectrum. For instance, the social brain theory posits that some animals, such as primates, evolved larger brains due to the cognitive

demands of social behavior (*129*). However, researchers of the social brain and other hypotheses rarely consider that microbial input may have facilitated, at least in some lineages, the evolution of sociability. Social behavior is a possible means to ensure the transmission of microbial symbionts from one animal to another, both within generations (horizontal transfer) and across generations (vertical transfer), to the benefit of the host animal and the microbes. This holobiont-level hypothesis is substantiated by evidence documenting how changes in gut microbiota composition can affect social behavior in laboratory animals and in some cases wild animals. Additionally, sociability can affect the microbiota both positively and negatively. Consequently, the impact of the microbiota on sociability and its neurobiological underpinnings has potentially enormous implications for ecology, evolution, and human biology. This association between microbiota and the CNS provides a biological framework to elucidate how complex behavioral patterns ranging from eusociability to asocial behaviors may have evolved across the animal kingdom. Moreover, it raises important considerations about the impact of certain lifestyle choices [such as diet, medication use (e.g., antibiotics), and relationships] on human health, while also helping to provide a greater understanding of the neurobiology underlying certain neuropsychiatric conditions and the potential development of future therapies. Although most attention has focused on the role of the gut microbiota, other host-microbiota interactions in different tissues (such as oral, skin, birth canal, etc.) may also contribute to social behaviors, and so it is important to examine the entire holobiont.

Expanding microbiome-sequencing analyses across the animal kingdom remains a major challenge but will allow for greater insight into how social behavior interacts with microbial symbionts within and across diverse ecosystems. It will also be important to identify commonalities in the mechanisms through which microbiota are transferred from one animal to another, so as to provide an evolutionary hologenomic framework explaining how symbiotic bacteria contribute to the spectrum of social behaviors observed throughout nature. Moreover, a greater emphasis is needed to establish causation through elucidating the functional pathways by which bacteria affect behaviors. To date, there has been an over-reliance on correlative associations between gut bacteria and behavior. If we are to ascertain how gut bacteria influence behaviors such as sociability, we must approach future studies with causal functionality as the primary objective. Finally, there is ample evidence that social behavior affects the composition of the microbiota, but the functional consequences of this on the social brain have yet to be elucidated. Such findings will provide insights into the evolution of social behavior and will also expand our understanding of disorders of the social brain.

REFERENCES AND NOTES

1. P. Mason, H. Shan, A valence-free definition of sociality as any violation of inter-individual independence. *Proc. R. Soc. B* **284**, 284 (2017). doi: 10.1098/rspb.2017.0948; pmid: 29118128
2. G. A. Matthews, K. M. Tye, Neural mechanisms of social homeostasis. *Ann. N.Y. Acad. Sci.* nyas.14016 (2019). doi: 10.1111/nyas.14016; pmid: 30875095
3. J. M. Brown, S. L. Hazen, Microbial modulation of cardiovascular disease. *Nat. Rev. Microbiol.* **16**, 171–181 (2018). doi: 10.1038/nrmicro.2017.149; pmid: 29307889
4. B. Han *et al*., Microbial Genetic Composition Tunes Host Longevity. *Cell* **169**, 1249–1262.e13 (2017). doi: 10.1016/j.cell.2017.05.036; pmid: 28622510
5. E. Patterson *et al*., Gut microbiota, obesity and diabetes. *Postgrad. Med. J.* **92**, 286–300 (2016). doi: 10.1136/postgradmedj-2015-133285; pmid: 26912499
6. J. A. Foster, K. A. McVey Neufeld, Gut-brain axis: How the microbiome influences anxiety and depression. *Trends Neurosci.* **36**, 305–312 (2013). doi: 10.1016/j.tins.2013.01.005; pmid: 23384445
7. M. Lyte, Microbial endocrinology: Host-microbiota neuroendocrine interactions influencing brain and behavior. *Gut Microbes* **5**, 381–389 (2014). doi: 10.4161/gmic.28682; pmid: 24690573
8. E. Sherwin, K. V. Sandhu, T. G. Dinan, J. F. Cryan, May the Force Be With You: The Light and Dark Sides of the Microbiota-Gut-Brain Axis in Neuropsychiatry. *CNS Drugs* **30**, 1019–1041 (2016). doi: 10.1007/s40263-016-0370-3; pmid: 27417321
9. G. L. Davidson, A. C. Cooke, C. N. Johnson, J. L. Quinn, The gut microbiome as a driver of individual variation in cognition and functional behaviour. *Philos. Trans. R. Soc. London Ser. B* **373**, 373 (2018). pmid: 30104431
10. R. M. Stilling, S. R. Bordenstein, T. G. Dinan, J. F. Cryan, Friends with social benefits: Host-microbe interactions as a driver of brain evolution and development? *Front. Cell. Infect. Microbiol.* **4**, 147 (2014). doi: 10.3389/fcimb.2014.00147; pmid: 25401092
11. I. Zilber-Rosenberg, E. Rosenberg, Role of microorganisms in the evolution of animals and plants: The hologenome theory of evolution. *FEMS Microbiol. Rev.* **32**, 723–735 (2008). doi: 10.1111/j.1574-6976.2008.00123.x; pmid: 18549407
12. J. D. Shropshire, S. R. Bordenstein, Speciation by Symbiosis: The Microbiome and Behavior. *mBio* **7**, e01785-15 (2016). doi: 10.1128/mBio.01785-15; pmid: 27034284
13. S. R. Bordenstein, K. R. Theis, Host Biology in Light of the Microbiome: Ten Principles of Holobionts and Hologenomes. *PLOS Biol.* **13**, e1002226 (2015). doi: 10.1371/journal.pbio.1002226; pmid: 26284777
14. K. R. Theis *et al*., Symbiotic bacteria appear to mediate hyena social odors. *Proc. Natl. Acad. Sci. U.S.A.* **110**, 19832–19837 (2013). doi: 10.1073/pnas.1306477110; pmid: 24218592
15. Q. Li *et al*., Synchronous evolution of an odor biosynthesis pathway and behavioral response. *Curr. Biol.* **23**, 11–20 (2013). doi: 10.1016/j.cub.2012.10.047; pmid: 23177478
16. M. E. Chafee *et al*., Decoupling of host-symbiont-phage coadaptations following transfer between insect species. *Genetics* **187**, 203–215 (2011). doi: 10.1534/genetics.110.120675; pmid: 20944019
17. S. A. Buffington *et al*., Microbial Reconstitution Reverses Maternal Diet-Induced Social and Synaptic Deficits in Offspring. *Cell* **165**, 1762–1775 (2016). doi: 10.1016/j.cell.2016.06.001; pmid: 27315483
18. J. Tung *et al*., Social networks predict gut microbiome composition in wild baboons. *eLife* **4**, e05224 (2015). doi: 10.7554/eLife.05224
19. J. G. P. Phillips, The Treatment of Melancholia by the Lactic Acid Bacillus. *J. Ment. Sci.* **56**, 422–430 (1910). doi: 10.1192/bjp.56.234.422
20. W. Han *et al*., A Neural Circuit for Gut-Induced Reward. *Cell* **175**, 665–678.e23 (2018). doi: 10.1016/j.cell.2018.08.049; pmid: 30245012
21. B. Bonaz, T. Bazin, S. Pellissier, The Vagus Nerve at the Interface of the Microbiota-Gut-Brain Axis. *Front. Neurosci.* **12**, 49 (2018). doi: 10.3389/fnins.2018.00049; pmid: 29467611
22. M. M. Kaelberer *et al*., A gut-brain neural circuit for nutrient sensory transduction. *Science* **361**, eaat5236 (2018). doi: 10.1126/science.aat5236; pmid: 30237325
23. S. Holmqvist *et al*., Direct evidence of Parkinson pathology spread from the gastrointestinal tract to the brain in rats. *Acta Neuropathol.* **128**, 805–820 (2014). doi: 10.1007/s00401-014-1343-6; pmid: 25296989
24. E. Svensson *et al*., Vagotomy and subsequent risk of Parkinson's disease. *Ann. Neurol.* **78**, 522–529 (2015). doi: 10.1002/ana.24448; pmid: 26031848
25. J. A. Bravo *et al*., Ingestion of Lactobacillus strain regulates emotional behavior and central GABA receptor expression in a mouse via the vagus nerve. *Proc. Natl. Acad. Sci. U.S.A.* **108**, 16050–16055 (2011). doi: 10.1073/pnas.1102999108; pmid: 21876150
26. P. Bercik *et al*., The anxiolytic effect of Bifidobacterium longum NCC3001 involves vagal pathways for gut-brain communication. *Neurogastroenterol. Motil.* **23**, 1132–1139 (2011). doi: 10.1111/j.1365-2982.2011.01796.x; pmid: 21988661
27. T. Poutahidis *et al*., Microbial symbionts accelerate wound healing via the neuropeptide hormone oxytocin. *PLOS ONE* **8**, e78898 (2013). doi: 10.1371/journal.pone.0078898; pmid: 24205344
28. P. Bercik *et al*., Chronic gastrointestinal inflammation induces anxiety-like behavior and alters central nervous system biochemistry in mice. *Gastroenterology* **139**, 2102–2112.e1 (2010). doi: 10.1053/j.gastro.2010.06.063; pmid: 20600016
29. A. Taj, N. Jamil, Bioconversion of Tyrosine and Tryptophan Derived Biogenic Amines by Neuropathogenic Bacteria. *Biomolecules* **8**, 10 (2018). doi: 10.3390/biom8010010; pmid: 29438351
30. V. V. Roshchina, New Trends and Perspectives in the Evolution of Neurotransmitters in Microbial, Plant, and Animal Cells. *Adv. Exp. Med. Biol.* **874**, 25–77 (2016). doi: 10.1007/978-3-319-20215-0_2; pmid: 26589213
31. T. M. Marques *et al*., Influence of GABA and GABA-producing Lactobacillus brevis DPC 6108 on the development of diabetes in a streptozotocin rat model. *Benef. Microbes* **7**, 409–420 (2016). doi: 10.3920/BM2015.0154; pmid: 27013462
32. G. Clarke *et al*., The microbiome-gut-brain axis during early life regulates the hippocampal serotonergic system in a sex-dependent manner. *Mol. Psychiatry* **18**, 666–673 (2013). doi: 10.1038/mp.2012.77; pmid: 22688187
33. D. Erny *et al*., Host microbiota constantly control maturation and function of microglia in the CNS. *Nat. Neurosci.* **18**, 965–977 (2015). doi: 10.1038/nn.4030; pmid: 26030851
34. M. van de Wouw *et al*., Short-chain fatty acids: Microbial metabolites that alleviate stress-induced brain-gut axis alterations. *J. Physiol.* **596**, 4923–4944 (2018). doi: 10.1113/JP276431; pmid: 30066368
35. B. B. Nankova, R. Agarwal, D. F. MacFabe, E. F. La Gamma, Enteric bacterial metabolites propionic and butyric acid modulate gene expression, including CREB-dependent catecholaminergic neurotransmission, in PC12 cells—Possible relevance to autism spectrum disorders. *PLOS ONE* **9**, e103740 (2014). doi: 10.1371/journal.pone.0103740; pmid: 25170769
36. D. F. MacFabe, N. E. Cain, F. Boon, K. P. Ossenkopp, D. P. Cain, Effects of the enteric bacterial metabolic product propionic acid on object-directed behavior, social behavior, cognition, and neuroinflammation in adolescent rats: Relevance to autism spectrum disorder. *Behav. Brain Res.* **217**, 47–54 (2011). doi: 10.1016/j.bbr.2010.10.005; pmid: 20937326
37. T. Arentsen *et al*., The bacterial peptidoglycan-sensing molecule Pglyrp2 modulates brain development and behavior. *Mol. Psychiatry* **22**, 257–266 (2017). doi: 10.1038/mp.2016.182; pmid: 27843150
38. Y. Zhan *et al*., Deficient neuron-microglia signaling results in impaired functional brain connectivity and social behavior. *Nat. Neurosci.* **17**, 400–406 (2014). doi: 10.1038/nn.3641; pmid: 24487234
39. L. H. Nelson, K. M. Lenz, Microglia depletion in early life programs persistent changes in social, mood-related, and locomotor behavior in male and female rats. *Behav. Brain Res.* **316**, 279–293 (2017). doi: 10.1016/j.bbr.2016.09.006; pmid: 27613230
40. A. C. Wong *et al*., Gut Microbiota Modifies Olfactory-Guided Microbial Preferences and Foraging Decisions in Drosophila.

Curr. Biol. **27**, 2397–2404.e4 (2017). doi: 10.1016/j.cub.2017.07.022; pmid: 28756953
41. A. François *et al.*, Olfactory epithelium changes in germfree mice. *Sci. Rep.* **6**, 24687 (2016). doi: 10.1038/srep24687; pmid: 27089944
42. B. J. Ashton, A. R. Ridley, E. K. Edwards, A. Thornton, Cognitive performance is linked to group size and affects fitness in Australian magpies. *Nature* **554**, 364–367 (2018). doi: 10.1038/nature25503; pmid: 29414945
43. A. Borbón-García, A. Reyes, M. Vives-Flórez, S. Caballero, Captivity Shapes the Gut Microbiota of Andean Bears: Insights into Health Surveillance. *Front. Microbiol.* **8**, 1316 (2017). doi: 10.3389/fmicb.2017.01316; pmid: 28751883
44. J. B. Clayton *et al.*, Captivity humanizes the primate microbiome. *Proc. Natl. Acad. Sci. U.S.A.* **113**, 10376–10381 (2016). doi: 10.1073/pnas.1521835113; pmid: 27573830
45. R. Nomoto *et al.*, Isolation and identification of *Bifidobacterium* species from feces of captive chimpanzees. *Biosci. Microbiota Food Health* **36**, 91–99 (2017). doi: 10.12938/bmfh.16-027; pmid: 28748130
46. J. L. Metcalf *et al.*, Evaluating the impact of domestication and captivity on the horse gut microbiome. *Sci. Rep.* **7**, 15497 (2017). doi: 10.1038/s41598-017-15375-9; pmid: 29138485
47. S. M. Rodríguez-Ruano *et al.*, The Hoopoe's Uropygial Gland Hosts a Bacterial Community Influenced by the Living Conditions of the Bird. *PLOS ONE* **10**, e0139734 (2015). doi: 10.1371/journal.pone.0139734; pmid: 26445111
48. H. Y. Jiang *et al.*, Diets Alter the Gut Microbiome of Crocodile Lizards. *Front. Microbiol.* **8**, 2073 (2017). doi: 10.3389/fmicb.2017.02073; pmid: 29118742
49. P. Engel, N. A. Moran, The gut microbiota of insects - diversity in structure and function. *FEMS Microbiol. Rev.* **37**, 699–735 (2013). doi: 10.1111/1574-6976.12025; pmid: 23692388
50. V. G. Martinson, J. Moy, N. A. Moran, Establishment of characteristic gut bacteria during development of the honeybee worker. *Appl. Environ. Microbiol.* **78**, 2830–2840 (2012). doi: 10.1128/AEM.07810-11; pmid: 22307297
51. V. G. Martinson *et al.*, A simple and distinctive microbiota associated with honey bees and bumble bees. *Mol. Ecol.* **20**, 619–628 (2011). doi: 10.1111/j.1365-294X.2010.04959.x; pmid: 21175905
52. D. Alberoni *et al.*, Impact of beneficial bacteria supplementation on the gut microbiota, colony development and productivity of Apis mellifera L. *Benef. Microbes* **9**, 269–278 (2018). pmid: 29380644
53. R. Kort *et al.*, Shaping the oral microbiota through intimate kissing. *Microbiome* **2**, 41 (2014). pmid: 25408893
54. K. A. Dill-McFarland *et al.*, Close social relationships correlate with human gut microbiota composition. *Sci. Rep.* **9**, 703 (2019). doi: 10.1038/s41598-018-37298-9; pmid: 30679677
55. I. L. Brito *et al.*, Transmission of human-associated microbiota along family and social networks. *Nat. Microbiol.* **4**, 964–971 (2019). doi: 10.1038/s41564-019-0409-6; pmid: 30911128
56. W. Z. Amaral *et al.*, Social Influences on Prevotella and the Gut Microbiome of Young Monkeys. *Psychosom. Med.* **79**, 888–897 (2017). doi: 10.1097/PSY.0000000000000454; pmid: 28178033
57. L. E. Grieneisen, J. Livermore, S. Alberts, J. Tung, E. A. Archie, Group Living and Male Dispersal Predict the Core Gut Microbiome in Wild Baboons. *Integr. Comp. Biol.* **57**, 770–785 (2017). doi: 10.1093/icb/icx046; pmid: 29048537
58. A. Raulo *et al.*, Social behaviour and gut microbiota in red-bellied lemurs (Eulemur rubriventer): In search of the role of immunity in the evolution of sociality. *J. Anim. Ecol.* **87**, 388–399 (2018). doi: 10.1111/1365-2656.12781; pmid: 29205327
59. A. C. Perofsky, R. J. Lewis, L. A. Abondano, A. Di Fiore, L. A. Meyers, Hierarchical social networks shape gut microbial composition in wild Verreaux's sifaka. *Proc. R. Soc. B* **284**, 284 (2017). doi: 10.1098/rspb.2017.2274; pmid: 29212730
60. A. H. Moeller *et al.*, Social behavior shapes the chimpanzee pan-microbiome. *Sci. Adv.* **2**, e1500997 (2016). doi: 10.1128/AEM.07810-11 pmid: 26824072
61. A. H. Moeller *et al.*, Sympatric chimpanzees and gorillas harbor convergent gut microbial communities. *Genome Res.* **23**, 1715–1720 (2013). doi: 10.1101/gr.154773.113; pmid: 23804402
62. A. Brune, C. Dietrich, The Gut Microbiota of Termites: Digesting the Diversity in the Light of Ecology and Evolution. *Annu. Rev. Microbiol.* **69**, 145–166 (2015). doi: 10.1146/annurev-micro-092412-155715; pmid: 26195303
63. F. Warnecke *et al.*, Metagenomic and functional analysis of hindgut microbiota of a wood-feeding higher termite. *Nature* **450**, 560–565 (2007). doi: 10.1038/nature06269; pmid: 18033299
64. A. Mikaelyan *et al.*, Diet is the primary determinant of bacterial community structure in the guts of higher termites. *Mol. Ecol.* **24**, 5284–5295 (2015). doi: 10.1111/mec.13376; pmid: 26348261
65. Y. Hongoh, Diversity and genomes of uncultured microbial symbionts in the termite gut. *Biosci. Biotechnol. Biochem.* **74**, 1145–1151 (2010). doi: 10.1271/bbb.100094; pmid: 20530908
66. R. J. Dillon, C. T. Vennard, A. K. A. Charnley, Gut bacteria produce components of a locust cohesion pheromone. *J. Appl. Microbiol.* **92**, 759–763 (2002). pmid: 11966918
67. N. Woodbury, G. Gries, Firebrats, *Thermobia domestica*, aggregate in response to the microbes *Enterobacter cloacae* and *Mycotypha microspora*. *Entomol. Exp. Appl.* **147**, 154–159 (2013). doi: 10.1111/eea.12054
68. N. Woodbury, M. Moore, G. Gries, Horizontal transmission of the microbial symbionts *Enterobacter cloacae* and *Mycotypha microspora* to their firebrat host. *Entomol. Exp. Appl.* **147**, 160–166 (2013). doi: 10.1111/eea.12057
69. A. Wada-Katsumata *et al.*, Gut bacteria mediate aggregation in the German cockroach. *Proc. Natl. Acad. Sci. U.S.A.* **112**, 15678–15683 (2015). pmid: 26644557
70. L. Xu, Q. Lou, C. Cheng, M. Lu, J. Sun, Gut-Associated Bacteria of Dendroctonus valens and their Involvement in Verbenone Production. *Microb. Ecol.* **70**, 1012–1023 (2015). doi: 10.1007/s00248-015-0625-4; pmid: 25985770
71. S. Leclaire, S. Jacob, L. K. Greene, G. R. Dubay, C. M. Drea, Social odours covary with bacterial community in the anal secretions of wild meerkats. *Sci. Rep.* **7**, 3240 (2017). doi: 10.1038/s41598-017-03356-x; pmid: 28607369
72. L. Amo *et al.*, Sex recognition by odour and variation in the uropygial gland secretion in starlings. *J. Anim. Ecol.* **81**, 605–613 (2012). doi: 10.1111/j.1365-2656.2011.01940.x; pmid: 22220811
73. V. O. Ezenwa, A. E. Williams, Microbes and animal olfactory communication: Where do we go from here? *BioEssays* **36**, 847–854 (2014). doi: 10.1002/bies.201400016; pmid: 24986361
74. D. Caillaud *et al.*, Gorilla susceptibility to Ebola virus: The cost of sociality. *Curr. Biol.* **16**, R489–R491 (2006). doi: 10.1016/j.cub.2006.06.017; pmid: 16824905
75. J. L. Tella, The evolutionary transition to coloniality promotes higher blood parasitism. *J. Evol. Biol.* **15**, 32–41 (2002). doi: 10.1046/j.1420-9101.2002.00375.x
76. L. Chiu *et al.*, Protective Microbiota: From Localized to Long-Reaching Co-Immunity. *Front. Immunol.* **8**, 1678 (2017). doi: 10.3389/fimmu.2017.01678; pmid: 29270167
77. G. Eberl, T. Pradeu, Towards a General Theory of Immunity? *Trends Immunol.* **39**, 261–263 (2018). pmid: 29229264
78. S. El Aidy, T. G. Dinan, J. F. Cryan, Gut Microbiota: The Conductor in the Orchestra of Immune-Neuroendocrine Communication. *Clin. Ther.* **37**, 954–967 (2015). doi: 10.1016/j.clinthera.2015.03.002; pmid: 25846319
79. P. Cotgreave, D. H. Clayton, *Comparative Analysis of Time Spent Grooming by Birds in Relation to Parasite Load* (Brill, 1994). doi: 10.1163/156853994X00424
80. L. K. Newbold *et al.*, Helminth burden and ecological factors associated with alterations in wild host gastrointestinal microbiota. *ISME J.* **11**, 663–675 (2017). doi: 10.1038/ismej.2016.153; pmid: 27983724
81. S. C. Lee *et al.*, Helminth colonization is associated with increased diversity of the gut microbiota. *PLOS Negl. Trop. Dis.* **8**, e2880 (2014). doi: 10.1371/journal.pntd.0002880; pmid: 24851867
82. L. A. Reynolds, B. B. Finlay, Worming Their Way into the Picture: Microbiota Help Helminths Modulate Host Immunity. *Immunity* **43**, 840–842 (2015). doi: 10.1016/j.immuni.2015.10.025; pmid: 26588776
83. H. Koch, P. Schmid-Hempel, Socially transmitted gut microbiota protect bumble bees against an intestinal parasite. *Proc. Natl. Acad. Sci. U.S.A.* **108**, 19288–19292 (2011). doi: 10.1073/pnas.1110474108; pmid: 22084077
84. A. Stow *et al.*, Antimicrobial defences increase with sociality in bees. *Biol. Lett.* **3**, 422–424 (2007). doi: 10.1098/rsbl.2007.0178; pmid: 17504731
85. S. Tragust *et al.*, Ants disinfect fungus-exposed brood by oral uptake and spread of their poison. *Curr. Biol.* **23**, 76–82 (2013). doi: 10.1016/j.cub.2012.11.034; pmid: 23246409
86. A. D. Kay *et al.*, A carbohydrate-rich diet increases social immunity in ants. *Proc. R. Soc. B* **281**, 20132374 (2014). doi: 10.1098/rspb.2013.2374; pmid: 24430844
87. M. T. Bailey *et al.*, Exposure to a social stressor alters the structure of the intestinal microbiota: Implications for stressor-induced immunomodulation. *Brain Behav. Immun.* **25**, 397–407 (2011). doi: 10.1016/j.bbi.2010.10.023; pmid: 21040780
88. A. Burokas *et al.*, Targeting the Microbiota-Gut-Brain Axis: Prebiotics Have Anxiolytic and Antidepressant-like Effects and Reverse the Impact of Chronic Stress in Mice. *Biol. Psychiatry* **82**, 472–487 (2017). doi: 10.1016/j.biopsych.2016.12.031; pmid: 28242013
89. I. I. Levin *et al.*, Stress response, gut microbial diversity and sexual signals correlate with social interactions. *Biol. Lett.* **12**, 20160352 (2016). pmid: 27354713
90. F. Sommer *et al.*, The Gut Microbiota Modulates Energy Metabolism in the Hibernating Brown Bear Ursus arctos. *Cell Rep.* **14**, 1655–1661 (2016). doi: 10.1016/j.celrep.2016.01.026; pmid: 26854221
91. R. M. Sapolsky, Social Status and Health in Humans and Other Animals. *Annu. Rev. Anthropol.* **33**, 393–418 (2004). doi: 10.1146/annurev.anthro.33.070203.144000
92. M. Romano, Gut Microbiota as a Trigger of Accelerated Directional Adaptive Evolution: Acquisition of Herbivory in the Context of Extracellular Vesicles, MicroRNAs and Inter-Kingdom Crosstalk. *Front. Microbiol.* **8**, 721 (2017). doi: 10.3389/fmicb.2017.00721; pmid: 28473829
93. M. P. Lombardo, Access to mutualistic endosymbiotic microbes: An underappreciated benefit of group living. *Behav. Ecol. Sociobiol.* **62**, 479–497 (2007). doi: 10.1007/s00265-007-0428-9
94. Z. L. Sabree, N. A. Moran, Host-specific assemblages typify gut microbial communities of related insect species. *Springerplus* **3**, 138 (2014). doi: 10.1186/2193-1801-3-138; pmid: 24741474
95. Z. L. Sabree *et al.*, Genome shrinkage and loss of nutrient-providing potential in the obligate symbiont of the primitive termite Mastotermes darwiniensis. *Appl. Environ. Microbiol.* **78**, 204–210 (2012). doi: 10.1128/AEM.06540-11; pmid: 22020505
96. J. Holt-Lunstad, T. B. Smith, M. Baker, T. Harris, D. Stephenson, Loneliness and social isolation as risk factors for mortality: A meta-analytic review. *Perspect. Psychol. Sci.* **10**, 227–237 (2015). doi: 10.1177/1745691614568352; pmid: 25910392
97. J. R. Kelly *et al.*, Transferring the blues: Depression-associated gut microbiota induces neurobehavioural changes in the rat. *J. Psychiatr. Res.* **82**, 109–118 (2016). doi: 10.1016/j.jpsychires.2016.07.019; pmid: 27491067
98. A. V. Golubeva *et al.*, Microbiota-related Changes in Bile Acid & Tryptophan Metabolism are Associated with Gastrointestinal Dysfunction in a Mouse Model of Autism. *EBioMedicine* **24**, 166–178 (2017). doi: 10.1016/j.ebiom.2017.09.020; pmid: 28965876
99. K. A. Neufeld, N. Kang, J. Bienenstock, J. A. Foster, Effects of intestinal microbiota on anxiety-like behavior. *Commun. Integr. Biol.* **4**, 492–494 (2011). doi: 10.4161/cib.15702; pmid: 21966581
100. J. S. Son *et al.*, Comparison of Fecal Microbiota in Children with Autism Spectrum Disorders and Neurotypical Siblings in the Simons Simplex Collection. *PLOS ONE* **10**, e0137725 (2015). doi: 10.1371/journal.pone.0137725; pmid: 26427004
101. S. M. Finegold, Desulfovibrio species are potentially important in regressive autism. *Med. Hypotheses* **77**, 270–274 (2011). doi: 10.1016/j.mehy.2011.04.032; pmid: 21592674
102. B. Góra *et al.*, Toxin profile of fecal Clostridium perfringens strains isolated from children with autism spectrum disorders. *Anaerobe* **51**, 73–77 (2018). doi: 10.1016/j.anaerobe.2018.03.005; pmid: 29526827
103. E. A. Mayer, D. Padua, K. Tillisch, Altered brain-gut axis in autism: Comorbidity or causative mechanisms? *BioEssays* **36**, 933–939 (2014). doi: 10.1002/bies.201400075; pmid: 25145752
104. E. A. Curran *et al.*, Association Between Obstetric Mode of Delivery and Autism Spectrum Disorder: A Population-Based Sibling Design Study. *JAMA Psychiatry* **72**, 935–942 (2015). doi: 10.1001/jamapsychiatry.2015.0846; pmid: 26107922
105. K. J. Davey *et al.*, Gender-dependent consequences of chronic olanzapine in the rat: Effects on body weight, inflammatory, metabolic and microbiota parameters.

Psychopharmacology **221**, 155–169 (2012). doi: 10.1007/s00213-011-2555-2; pmid: 22234378
106. B. J. Varian *et al*., Microbial lysate upregulates host oxytocin. *Brain Behav. Immun.* **61**, 36–49 (2017). doi: 10.1016/j.bbi.2016.11.002; pmid: 27825953
107. L. Tabouy *et al*., Dysbiosis of microbiome and probiotic treatment in a genetic model of autism spectrum disorders. *Brain Behav. Immun.* **73**, 310–319 (2018). doi: 10.1016/j.bbi.2018.05.015; pmid: 29787855
108. M. Sgritta *et al*., Mechanisms Underlying Microbial-Mediated Changes in Social Behavior in Mouse Models of Autism Spectrum Disorder. *Neuron* **101**, 246–259.e6 (2019). doi: 10.1016/j.neuron.2018.11.018; pmid: 30522820
109. E. Y. Hsiao *et al*., Microbiota modulate behavioral and physiological abnormalities associated with neurodevelopmental disorders. *Cell* **155**, 1451–1463 (2013). doi: 10.1016/j.cell.2013.11.024; pmid: 24315484
110. H. M. Wexler, Bacteroides: The good, the bad, and the nitty-gritty. *Clin. Microbiol. Rev.* **20**, 593–621 (2007). doi: 10.1128/CMR.00008-07; pmid: 17934076
111. C. L. Sears, Enterotoxigenic Bacteroides fragilis: A rogue among symbiotes. *Clin. Microbiol. Rev.* **22**, 349–369 (2009). doi: 10.1128/CMR.00053-08; pmid: 19366918
112. J. R. Kelly *et al*., Lost in translation? The potential psychobiotic Lactobacillus rhamnosus (JB-1) fails to modulate stress or cognitive performance in healthy male subjects. *Brain Behav. Immun.* **61**, 50–59 (2017). doi: 10.1016/j.bbi.2016.11.018; pmid: 27865949
113. H. M. R. T. Parracho *et al*., A double-blind, placebo-controlled, crossover-designed probiotic feeding study in children diagnosed with autistic spectrum disorders. *Int. J. Probiotics Prebiotics* **5**, 69–74 (2010).
114. S. Y. Shaaban *et al*., The role of probiotics in children with autism spectrum disorder: A prospective, open-label study. *Nutr. Neurosci.* **21**, 676–681 (2018). doi: 10.1080/1028415X.2017.1347746; pmid: 28686541
115. D. W. Kang *et al*., Microbiota Transfer Therapy alters gut ecosystem and improves gastrointestinal and autism symptoms: An open-label study. *Microbiome* **5**, 10 (2017). doi: 10.1186/s40168-016-0225-7; pmid: 28122648
116. K. V. Sandhu *et al*., Feeding the microbiota-gut-brain axis: Diet, microbiome, and neuropsychiatry. *Transl. Res.* **179**, 223–244 (2017). doi: 10.1016/j.trsl.2016.10.002; pmid: 27832936
117. C. G. de Theije *et al*., Dietary long chain n-3 polyunsaturated fatty acids prevent impaired social behaviour and normalize brain dopamine levels in food allergic mice. *Neuropharmacology* **90**, 15–22 (2015). doi: 10.1016/j.neuropharm.2014.11.001; pmid: 25445491
118. M. M. Pusceddu *et al*., N-3 Polyunsaturated Fatty Acids (PUFAs) Reverse the Impact of Early-Life Stress on the Gut Microbiota. *PLOS ONE* **10**, e0139721 (2015). doi: 10.1371/journal.pone.0139721; pmid: 26426902
119. M. Nemeth *et al*., Sex-specific effects of dietary fatty acids on saliva cortisol and social behavior in guinea pigs under different social environmental conditions. *Biol. Sex Differ.* **7**, 51 (2016). doi: 10.1186/s13293-016-0107-5; pmid: 27688870
120. R. C. Robertson *et al*., Omega-3 polyunsaturated fatty acids critically regulate behaviour and gut microbiota development in adolescence and adulthood. *Brain Behav. Immun.* **59**, 21–37 (2017). doi: 10.1016/j.bbi.2016.07.145; pmid: 27423492
121. C. Lin *et al*., Omega-3 fatty acids regulate NLRP3 inflammasome activation and prevent behavior deficits after traumatic brain injury. *Exp. Neurol.* **290**, 115–122 (2017). doi: 10.1016/j.expneurol.2017.01.005; pmid: 28077335
122. C. S. Model *et al*., Omega-3 fatty acids alter behavioral and oxidative stress parameters in animals subjected to fenproporex administration. *Metab. Brain Dis.* **29**, 185–192 (2014). doi: 10.1007/s11011-013-9473-4; pmid: 24385143
123. C. O. Bondi *et al*., Adolescent behavior and dopamine availability are uniquely sensitive to dietary omega-3 fatty acid deficiency. *Biol. Psychiatry* **75**, 38–46 (2014). doi: 10.1016/j.biopsych.2013.06.007; pmid: 23890734
124. G. P. Amminger *et al*., Omega-3 fatty acids supplementation in children with autism: A double-blind randomized, placebo-controlled pilot study. *Biol. Psychiatry* **61**, 551–553 (2007). doi: 10.1016/j.biopsych.2006.05.007; pmid: 16920077
125. S. Bent, K. Bertoglio, P. Ashwood, A. Bostrom, R. L. Hendren, A pilot randomized controlled trial of omega-3 fatty acids for autism spectrum disorder. *J. Autism Dev. Disord.* **41**, 545–554 (2011). doi: 10.1007/s10803-010-1078-8; pmid: 20683766
126. A. M. Haagensen *et al*., High fat, low carbohydrate diet limit fear and aggression in Göttingen minipigs. *PLOS ONE* **9**, e93821 (2014). doi: 10.1371/journal.pone.0093821 pmid: 24740321
127. J. R. Kaplan *et al*., Demonstration of an association among dietary cholesterol, central serotonergic activity, and social behavior in monkeys. *Psychosom. Med.* **56**, 479–484 (1994). doi: 10.1097/00006842-199411000-00001; pmid: 7532867
128. R. Grimaldi *et al*., A prebiotic intervention study in children with autism spectrum disorders (ASDs). *Microbiome* **6**, 133 (2018). doi: 10.1186/s40168-018-0523-3; pmid: 30071894
129. R. I. Dunbar, The social brain hypothesis and its implications for social evolution. *Ann. Hum. Biol.* **36**, 562–572 (2009). doi: 10.1080/03014460902960289; pmid: 19575315
130. L. Desbonnet, G. Clarke, F. Shanahan, T. G. Dinan, J. F. Cryan, Microbiota is essential for social development in the mouse. *Mol. Psychiatry* **19**, 146–148 (2014). doi: 10.1038/mp.2013.65; pmid: 23689536
131. T. Arentsen, H. Raith, Y. Qian, H. Forssberg, R. Diaz Heijtz, Host microbiota modulates development of social preference in mice. *Microb. Ecol. Health Dis.* **26**, 29719 (2015). pmid: 26679775
132. C. D'Mello *et al*., Probiotics Improve Inflammation-Associated Sickness Behavior by Altering Communication between the Peripheral Immune System and the Brain. *J. Neurosci.* **35**, 10821–10830 (2015). doi: 10.1523/JNEUROSCI.0575-15.2015; pmid: 26224864
133. C. S. M. Cowan *et al*., Gutsy Moves: The Amygdala as a Critical Node in Microbiota to Brain Signaling. *BioEssays* **40**, 10.1002/bies.201700172 (2018). doi: 10.1002/bies.201700172; pmid: 29148060
134. L. Desbonnet *et al*., Gut microbiota depletion from early adolescence in mice: Implications for brain and behaviour. *Brain Behav. Immun.* **48**, 165–173 (2015). doi: 10.1016/j.bbi.2015.04.004; pmid: 25866195
135. F. Guida *et al*., Antibiotic-induced microbiota perturbation causes gut endocannabinoidome changes, hippocampal neuroglial reorganization and depression in mice. *Brain Behav. Immun.* **67**, 230–245 (2018). doi: 10.1016/j.bbi.2017.09.001; pmid: 28890155
136. X. Wang *et al*., Effects of β-diketone antibiotic mixtures on behavior of zebrafish (Danio rerio). *Chemosphere* **144**, 2195–2205 (2016). doi: 10.1016/j.chemosphere.2015.10.120; pmid: 26595314
137. G. Sharon *et al*., Commensal bacteria play a role in mating preference of Drosophila melanogaster. *Proc. Natl. Acad. Sci. U.S.A.* **107**, 20051–20056 (2010). pmid: 21041648
138. M. A. Najarro, M. Sumethasorn, A. Lamoureux, T. L. Turner, Choosing mates based on the diet of your ancestors: Replication of non-genetic assortative mating in Drosophila melanogaster. *PeerJ* **3**, e1173 (2015). doi: 10.7717/peerj.1173; pmid: 26339551
139. A. S. Brown, The environment and susceptibility to schizophrenia. *Prog. Neurobiol.* **93**, 23–58 (2011). doi: 10.1016/j.pneurobio.2010.09.003; pmid: 20955757
140. R. J. Dillon, V. M. Dillon, The gut bacteria of insects: Nonpathogenic interactions. *Annu. Rev. Entomol.* **49**, 71–92 (2004). doi: 10.1146/annurev.ento.49.061802.123416; pmid: 14651457
141. L. Borrelli *et al*., Probiotic modulation of the microbiota-gut-brain axis and behaviour in zebrafish. *Sci. Rep.* **6**, 30046 (2016). doi: 10.1038/srep30046; pmid: 27416816
142. S. Kulkarni, P. Heeb, Social and sexual behaviours aid transmission of bacteria in birds. *Behav. Processes* **74**, 88–92 (2007). doi: 10.1016/j.beproc.2006.10.005; pmid: 17118574
143. C. M. Benskin, G. Rhodes, R. W. Pickup, K. Wilson, I. R. Hartley, Diversity and temporal stability of bacterial communities in a model passerine bird, the zebra finch. *Mol. Ecol.* **19**, 5531–5544 (2010). doi: 10.1111/j.1365-294X.2010.04892.x; pmid: 21054607
144. R. Osawa, W. Blanshard, P. O'Callaghan, Microbiological Studies of the Intestinal Microflora of the Koala, Phascolarctos-Cinereus. 2. Pap, a Special Maternal Feces Consumed by Juvenile Koalas. *Aust. J. Zool.* **41**, 611–620 (1993). doi: 10.1071/ZO9930611
145. E. A. McKenney, M. Ashwell, J. E. Lambert, V. Fellner, Fecal microbial diversity and putative function in captive western lowland gorillas (Gorilla gorilla), common chimpanzees (Pan troglodytes), Hamadryas baboons (Papio hamadryas) and binturongs (Arctictis binturong). *Integr. Zool.* **9**, 557–569 (2014). doi: 10.1111/1749-4877.12112; pmid: 25236539
146. E. A. McKenney, A. Rodrigo, A. D. Yoder, Patterns of gut bacterial colonization in three primate species. *PLOS ONE* **10**, e0124618 (2015). doi: 10.1371/journal.pone.0124618; pmid: 25970595
147. D. Rothschild *et al*., Environment dominates over host genetics in shaping human gut microbiota. *Nature* **555**, 210–215 (2018). doi: 10.1038/nature25973; pmid: 29489753
148. S. Cussotto *et al*., Psychotropics and the Microbiome: A Chamber of Secrets. *Psychopharmacology* **236**, 1411–1432 (2019). doi: 10.1007/s00213-019-5185-8
149. J. F. Cryan *et al*., The Microbiota-Gut-Brain Axis. *Physiol. Rev.* **99**, 1877–2013 (2019). doi: 10.1152/physrev.00018.2018

ACKNOWLEDGMENTS

We thank R. Stilling, G. Moloney, A. P. Ventura Da Silva, D. Slattery, and G. Davidson for helpful comments. **Funding:** Supported by a Science Foundation Ireland (SFI) grant to APC Microbiome Ireland through the Irish Government's National Development Plan (grant SFI/12/RC/2273_P2), the Irish Health Research Board, Enterprise Ireland, and the Department of Agriculture, Food and the Marine (T.G.D. and J.F.C.); European Research Council Consolidator grant 617509 (J.L.Q.); and NIH grants R21 AI133522 and RO1 AI132581, NSF grant 1456778, and the Vanderbilt Microbiome Initiative (S.R.B.). **Competing interests:** T.G.D. and J.F.C. receive research funding from 4D-Pharma, Mead Johnson, Suntory Wellness, Nutricia, Cremo, and DuPont. T.G.D. has been an invited speaker at conferences organized by Servier, Lundbeck, Janssen, and AstraZeneca. J.F.C. has been an invited speaker at conferences organized by Mead Johnson, Nutricia, Alkermes, and Janssen. E.S., S.R.B., and J.L.Q. declare no competing interests.

10.1126/science.aar2016

Science

Microbiota and the social brain

Eoin Sherwin, Seth R. Bordenstein, John L. Quinn, Timothy G. Dinan and John F. Cryan

Science **366** (6465), eaar2016.
DOI: 10.1126/science.aar2016

Animal sociability through microbes

Accumulating evidence suggests that the microbiota living in and on animals has important functions in the social architecture of those animals. Sherwin *et al.* review how the microbiota might facilitate neurodevelopment, help program social behaviors, and facilitate communication in various animal species, including humans. Understanding the complex relationship between microbiota and animal sociability may also identify avenues for treating social disorders in humans.

Science, this issue p. eaar2016