

REVIEW



## Microbial metabolites as engines of behavioral variation across animals

Eric Siaw Ntiri<sup>a</sup> and Adam Chun Nin Wong<sup>a,b</sup>

<sup>a</sup>Entomology and Nematology Department, University of Florida, Gainesville, FL, USA; <sup>b</sup>Genetics Institute, University of Florida, Gainesville, FL, USA

### ABSTRACT

The microbiome, especially that present in the gut, has emerged as a key modulator of animal behavior. However, the extent of its influence across species and behavioral repertoires, as well as the underlying mechanisms, remains poorly understood. Increasing evidence suggests that microbial metabolites play an important role in driving behavioral variation. In this review, we synthesize findings from vertebrates to invertebrates, spanning both model and non-model organisms, to define key groups of microbial-derived metabolites involved in modulating seven distinct behaviors: nutrition, olfaction, circadian rhythms, reproduction, locomotion, aggression, and social interactions. We discuss how these microbial metabolites interact with host chemosensory systems, neurotransmitter signaling, and epigenetic modifications to shape behavior. Additionally, we highlight critical gaps in mechanistic understanding, including the need to map additional host receptors and signaling pathways, as well as the untapped potential of microbial biosynthetic gene clusters as sources for novel bioactive compounds. Advancing these areas will enhance understanding of the microbiome's role in behavioral modulation and open new avenues for microbiome-based interventions for behavioral disorders.

### ARTICLE HISTORY

Received 6 February 2025  
Revised 7 April 2025  
Accepted 28 April 2025

### KEYWORDS

Microbiome; metabolites; symbiosis; behavior; gut-brain axis



## Introduction

From Pavlov's classic experiment on conditioned reflexes to von Frisch's characterization of the honey bee's waggle dance, understanding the drivers of behavior has long been a central pursuit in biology. Historically, research has centered on the interplay between genes and external environmental factors. However, our understanding is evolving with the recognition that the pathways leading from genes to behavior can be modified by microbial communities residing within organisms, and new evidence suggesting that how animals perceive and respond to environmental stimuli could be molded by their microbial experience.

As our appreciation of the microbiome-behavior connection deepens, researchers are increasingly focusing on unraveling the chemical communications that underline microbiome-mediated behavioral modulation. Microbes possess biosynthetic gene clusters capable of producing a remarkable diversity of bioactive metabolites.<sup>1–3</sup> Interestingly, many of these gene clusters are silent under standard laboratory

growth conditions,<sup>4–6</sup> signifying a vast untapped potential for discovering bioactive compounds.

Microbiomes associated with animal hosts can produce metabolites *de novo* or make use of host resources. These metabolites can be synthesized independently or through synergistic interactions between intra-kingdom species (e.g., bacteria-bacteria) or inter-kingdom species (e.g., bacterial-fungi) interactions.<sup>4,5,7–9</sup> For instance, microbes can ferment host-derived carbohydrates and proteins to generate key metabolites such as short-chain fatty acids (SCFAs) and branched-chain fatty acids (BCFAs), which are integral to metabolic and immune functions.<sup>10–12</sup> Additionally, some microbes actively contribute to the biosynthesis of neurotransmitters and neuromodulators, including dopamine, norepinephrine, serotonin, gamma-aminobutyric acid (GABA), acetylcholine, and histamine.<sup>13–16</sup> The vast diversity of microbial metabolites suggests that the microbiome exerts its effects on host behavior through multiple signaling pathways.

**CONTACT** Adam Chun Nin Wong  [adamcnwong@ufl.edu](mailto:adamcnwong@ufl.edu)  Entomology and Nematology Department, University of Florida, 1881 Natural Area Drive, Bldg. 970 PO Box 110620, Gainesville 32611-0620, FL, USA

© 2025 The Author(s). Published with license by Taylor & Francis Group, LLC.

This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0/>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. The terms on which this article has been published allow the posting of the Accepted Manuscript in a repository by the author(s) or with their consent.



Given the complexity of mammalian systems, studies using simpler models can provide valuable mechanistic insights into microbiome-behavior interactions.<sup>17</sup> Model organisms such as the *Caenorhabditis elegans* and *Drosophila melanogaster* have been instrumental in uncovering fundamental biological principles that later translated into mammals, including the roles of Toll-like receptors in innate immunity,<sup>18</sup> microRNA-mediated post-transcriptional gene regulation,<sup>19,20</sup> and the molecular mechanisms of circadian rhythms.<sup>21,22</sup> Their relatively simple nervous systems, combined with well-characterized microbiomes and genetic tractability, facilitate precise dissection of microbial metabolites effects on host behavior. Other non-mammalian systems, including certain insect and avian species, are also increasingly studied for their unique advantages. Some species offer closer physiological parallels to mammals,<sup>23</sup> while others allow high-throughput behavioral assays in ecologically relevant contexts.<sup>24</sup> Although findings from non-mammalian models must be extrapolated cautiously, given key biological differences such as the lack of adaptive immunity in invertebrates and variations in behavioral complexity, integrating findings across diverse systems offers complementary perspectives in understanding microbiome-mediated behavioral modulation.

In this review, we synthesize evidence on how bacterial and fungal bioactive compounds modulate behaviors including feeding and foraging, olfaction, circadian rhythms, reproduction, locomotion, aggression, and social interactions (Figure 1). We also discuss mechanisms by which microbial metabolites interact with host chemosensory systems, neurotransmitter signaling, and epigenetic modifications to alter behavior, and identify key areas for future research.

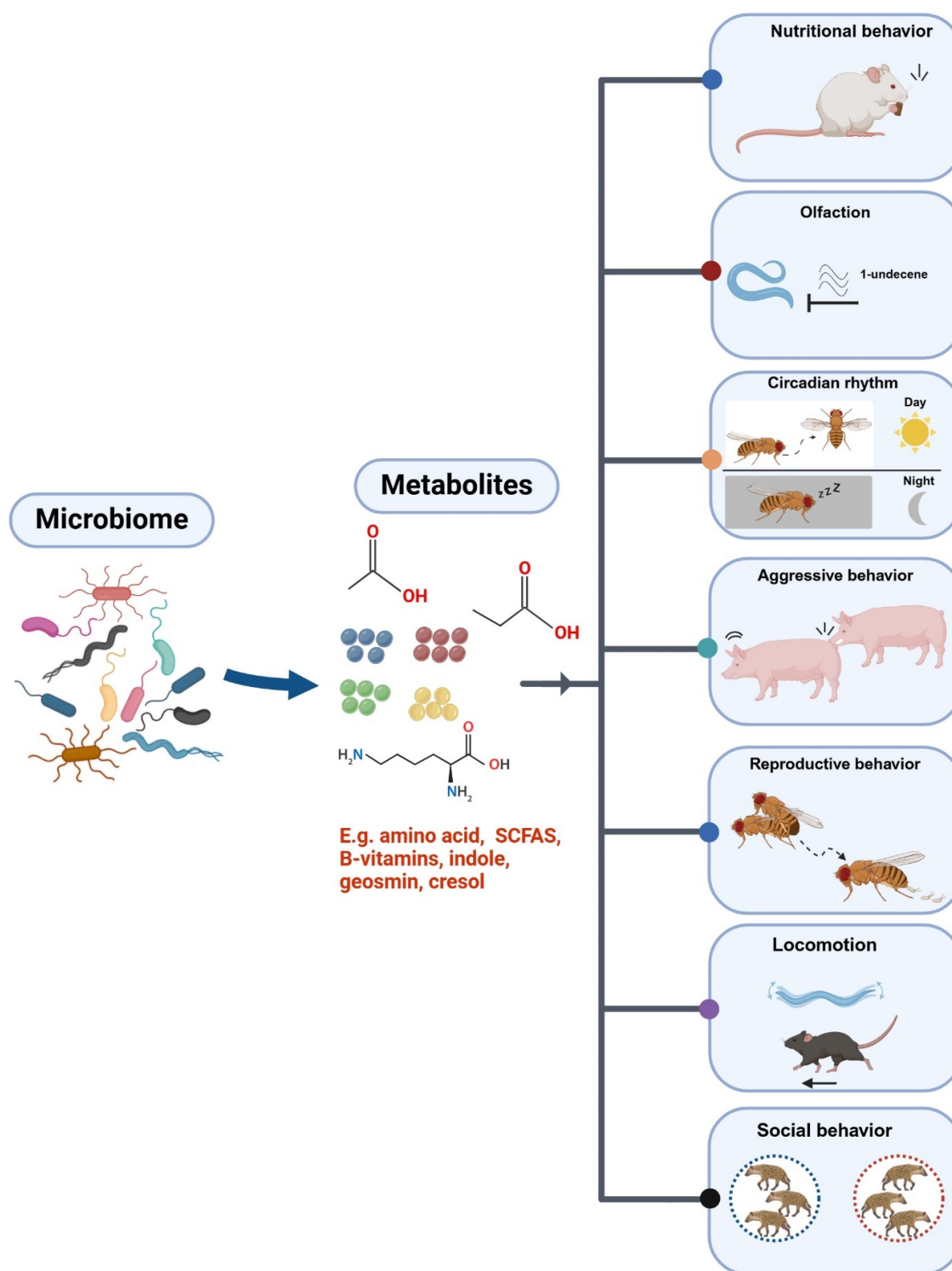
## Nutritional behaviors

The need for nutrients to support reproduction, growth, and development manifests in various nutritional behaviors, including foraging and feeding.<sup>25–29</sup> These behaviors have long been studied through the frameworks of optimal foraging theory (OFT) and nutritional ecology, which seek to explain how animals navigate complex dietary

landscapes to optimize fitness.<sup>30</sup> OFT conceptualizes foraging as an economic decision-making process, balancing the energetic costs and benefits of food acquisition, while nutritional ecology, particularly the geometric framework model, emphasizes the role of macronutrient balance in shaping dietary choices. These models are incomplete without considering the microbiome's role.

One of the most direct ways the microbiome shapes nutritional behavior is through nutrient provisioning. Microbes can serve as direct food sources for certain animal species,<sup>31–33</sup> as seen in the nematode *C. elegans* consuming bacteria from the phyla Proteobacteria, Bacteroidetes, Firmicutes, and Actinobacteria<sup>34</sup> and in *Drosophila* that feed on various yeast species.<sup>35</sup> Beyond being a passive food source, the microbiome actively contributes to the host's metabolic profile by synthesizing or transforming nutrients. For example, the gut bacterium *Acetobacter orientalis* provides branched-chain amino acids such as leucine and isoleucine, which are important for larval growth in *Drosophila*.<sup>36</sup> The gut microbiome also supplies B-vitamins, particularly riboflavin and thiamine, to support fly development under nutrient-limited conditions.<sup>37,38</sup> Other invertebrate examples include gut bacteria *Enterobacteriaceae* in the Mediterranean fruit fly that can fix atmospheric nitrogen,<sup>39</sup> *Blattabacterium* in cockroaches<sup>40</sup> and the microbiome in herbivorous turtle ants<sup>41</sup> that recycle nitrogen from urea and uric acid to meet the hosts' nitrogen needs. In mice, *Lactobacillus intestinalis* converts dietary vitamin A into retinoid metabolites.<sup>42</sup> Separately, in rats, high levels of vitamin A reduced sucrose preference and food intake.<sup>43,44</sup> As retinoid signaling can influence appetite regulation,<sup>45</sup> microbial metabolism of vitamin A may play a role in shaping feeding behavior. In humans, a comprehensive genomic analysis revealed that 40–65% of common gut bacteria possess biosynthetic pathways for essential B-vitamins.<sup>46</sup> The analysis suggests that the gut bacteria engage in “cross-feeding”, whereby species that lack the ability to synthesize certain B vitamins rely on those produced by others. The human gut microbiome also consists of amino acid auxotrophies that depend on the amino acids synthesized by other members.<sup>47</sup> These cooperative exchanges highlight the complexity of microbial community





**Figure 1.** Microbial metabolites influence diverse host behaviors. This schematic highlights the interplay between microbiome-derived metabolites and host behaviors, illustrating the broad impact of microbial metabolism on behavioral modulation. Created in <https://BioRender.com>.

interactions in shaping the host's overall nutrient balance.<sup>48–50</sup>

Despite the growing understanding of microbial contributions to host nutrition, evidence

linking microbial nutrient provisioning to host feeding behavior remains scarce. Notable insights were yielded from studies on *D. melanogaster*<sup>51</sup> demonstrating that dietary deprivation of any



single essential amino acid (eAA) triggered a stronger appetite for amino acid-rich food. The response was mitigated by the presence of the commensal bacteria *Acetobacter pomorum* and *Lactobacillus* species, without measurable changes in the host's amino acid levels. This suggests that the gut bacteria influence feeding behavior through mechanisms beyond mere nutrient supplementation. Further research by<sup>8</sup> uncovered that *Acetobacter* uses lactate produced by *Lactobacillus* to generate essential amino acids. This cross-feeding enables *Lactobacillus* to persist in nutrient-imbalanced diets. Lactate was found to be necessary and sufficient for *Acetobacter* to alter the fly's protein appetite, thus establishing a mechanistic link between microbial metabolic interactions and host feeding preference.

Besides nutrient provisioning, the microbiome influences nutritional behaviors by producing metabolites that interact with the host's endocrine and nervous systems. For example, high-fat diet-induced obesity in female mice can be mitigated by a dietary intervention involving high-fiber inulin, which restructures the gut microbiome and increases short-chain fatty acid (SCFA) levels, leading to reduced food intake and ameliorated postpartum stress behaviors.<sup>52</sup> In honey bees, conventional bees exhibited significantly higher sensitivity to sucrose compared to germ-free bees, a phenomenon potentially linked to differential SCFA levels and insulin signaling.<sup>53</sup> Oleoylethanolamide, a metabolite partially synthesized from dietary oleic acid by gut microbes, regulates satiety and energy balance in mice by activating intestinal G protein-coupled receptor 119 and peroxisome proliferator-activated receptor alpha (PPAR- $\alpha$ ).<sup>54,55</sup>

Some microbial metabolites shape nutritional behaviors by modulating gut hormones (Table 1). In mammals, enteroendocrine cells produce hormones like peptide YY (PYY) and glucagon-like peptide-1 (GLP-1) that communicate the body's nutritional status to the nervous system, thereby regulating appetite and satiety.<sup>67,68</sup> SCFAs such as butyrate, propionate, and acetate have been shown to impact the production of these gut hormones. For example, the administration of SCFAs in rodents increases PYY and GLP-1 levels,<sup>56–58</sup> and similar effects have been observed in pigs administered propionate.<sup>59</sup> Microbially-derived tryptophan catabolites, such as indole, have been shown to simulate GLP-1 production, contributing to appetite suppression.<sup>60,61</sup> Secondary bile acids derived from microbial processing of primary bile acids<sup>69</sup> have also been shown to regulate postprandial GLP-1 secretion. In microbiome-depleted (germ-free or antibiotic-treated) mice, fasting levels of secondary bile acids including  $\omega$ -muricholic acid ( $\omega$ MCA), hyocholic acid (HCA), deoxycholic acid (DCA), and lithocholic acid (LCA) were reduced in the ileum, coupling with an impaired GLP-1 response to oil intake. Interestingly, supplementation with  $\omega$ MCA and HCA directly stimulated GLP-1 secretion via the TGR5 receptor in microbiome-depleted mice and primary ileal cell cultures. By contrast, DCA failed to induce GLP-1 in ileal cells from microbiome-depleted mice, implying its effect on GLP-1 is microbiome-dependent.<sup>62</sup>

Beyond the gut, metabolites impacting the host's neural circuits play a significant role in regulating nutritional behavior.<sup>70</sup> For example, administration of butyrate, propionate, and acetate, was shown to suppress food intake via the vagal afferents in a dose-dependent manner in mice.<sup>71</sup>

**Table 1.** Gut hormones in mammals and their insect homologs implicated in nutritional behavior and the microbial metabolites that modulate their release.

Mammalian gut hormones/peptides	Insect gut hormones/peptides	Microbial metabolites that modulate gut hormone release	Refs
<ul style="list-style-type: none"> <li>Glucagon-like peptide-1</li> </ul>	<ul style="list-style-type: none"> <li>Adipokinetic hormone</li> </ul>	<ul style="list-style-type: none"> <li>SCFAs (acetic, propionic, butyric acids)</li> <li>Tryptophan catabolites (e.g. indole)</li> <li>Secondary bile Acids (deoxycholic acid, lithocholic acid)</li> <li>SCFAs (acetic, propionic, butyric acids)</li> </ul>	56–59 60,61 62 56–59
<ul style="list-style-type: none"> <li>Peptide YY</li> </ul>	<ul style="list-style-type: none"> <li>Neuropeptide F</li> <li>Short neuropeptide F</li> </ul>		
<ul style="list-style-type: none"> <li>Serotonin</li> <li>Cholecystokinin</li> <li>Leptin</li> <li>Insulin</li> </ul>	<ul style="list-style-type: none"> <li>Serotonin</li> <li>Sulfakinins</li> <li>Unpaired 1 &amp; 2</li> <li>Insulin</li> </ul>	<ul style="list-style-type: none"> <li>SCFAs (acetic, propionic, butyric acids)</li> <li>SCFAs (acetic, propionic, butyric acids)</li> <li>SCFAs (acetic, propionic, butyric acids)</li> <li>SCFAs (acetate, malate)</li> </ul>	63,64 65 66 53



Muropeptides, components of bacteria cell wall,<sup>72</sup> target brain neurons expressing the Nod2 receptor to control feeding behavior in mice. Older female mice (7–8 months) that lacked Nod2 consumed more food than their wild type counterparts.<sup>73</sup>

Collectively, these findings demonstrate that the gut microbiome not only supplements host nutrition by providing essential nutrients but also actively shapes nutritional behaviors through metabolic interactions acting on endocrine signaling and neural pathways. As the microbiome is plastic and individualized, its differences could contribute to variation in nutritional behaviors, such as dietary preferences and feeding habits, across individuals and species.

## Olfaction

Olfaction, the sensory process through which organisms detect and interpret volatile chemical signals from the environment, is a crucial modality that guides behaviors essential for ecological fitness, such as finding food, mates, nesting sites, and detecting threats.<sup>74–78</sup> Olfactory-guided behavior can be innate or learnt, reflecting a complex interaction between genetic predisposition and environmental experience.<sup>74</sup> Increasing evidence suggests that microbes can modulate host olfaction at multiple levels.<sup>79–81</sup> Intrinsically, the microbiome can influence the structure and function of host olfactory tissues.<sup>82,83</sup> For instance, germ-free mice exhibited a thinner cilia layer, reduced cellular turnover, and heightened neuronal responses to odorants in the olfactory epithelium, compared to conventional mice.<sup>83</sup> These changes are associated with reduced expression of xenobiotic metabolizing enzymes. It was proposed that without microbial metabolites to compete, fewer enzymes are required to clear odorants, resulting in longer-lasting odorant responses. However, since germ-free mice lack both gut and nasal microbiomes, it remains unclear whether these effects are driven by the gut microbiome acting remotely via circulating metabolites, or nasal microbiome acting locally on the tissues. Further research is needed to distinguish these contributions.

Microbial metabolism of host-derived compounds can further influence olfactory perception and behavior. For example, inhibition of

trimethylamine N-oxide (TMAO) production by gut microbes using the inhibitor iodomethylcholine (IMC) impaired mice's ability to detect and respond to certain odors, demonstrated by delayed detection of hidden food and reduced interest in scents like tap water and almonds. IMC-treated mice also had difficulty distinguishing between familiar and novel social partners, leading to decreased social interactions.<sup>84</sup> In honey bees, the gut microbe *Lactobacillus* regulates tryptophan metabolism to indole that activates the aryl hydrocarbon receptor, influencing bee olfactory learning and memory. Conventional bees showed a higher learning rate in the association of nonanol to sucrose reward, compared to antibiotic-treated and axenic bees.<sup>85</sup>

New evidence suggests that microbial effects on olfaction can manifest over longer periods, such as priming the olfactory system, leading to sustained changes in preferences and behaviors. In *Drosophila*, early-life exposure to specific gut symbionts, particularly *Acetobacter*, has been shown to enhance behavioral attraction toward the microbes, suggesting that microbial experience during development may play a key role in shaping host olfactory preferences.<sup>86</sup> The effect might be attributed to exposure to acetoin produced by egg-associated microbes.<sup>87</sup> Additionally, flies fed on indole-3-acetic acid produced by *Pseudomonas juntendi* showed higher attraction to ethanol but lower attraction to 1-octanol, highlighting the potential role of microbial metabolites in shaping olfactory preferences linked to addiction-related behaviors.<sup>88</sup> In *C. elegans*, the gut bacterium *Providencia* produces tyramine, which is converted by a host enzyme into octopamine. This neurotransmitter then acts on the OCTR-1 receptor on ASH nociceptive neurons, modulating the worm's aversive olfactory response.<sup>89</sup>

Microbes in the external environment also shape olfactory behavior through the release of volatile metabolites. For example, in *D. melanogaster*, the microbial metabolite geosmin is detected by a specific olfactory receptor (Or56a), triggering a robust avoidance response. This behavior is believed to be an evolutionary adaptation to avoid harmful microorganisms.<sup>90</sup> Similarly, in *C. elegans*, toxic bacterial metabolites such as tambjamine YP1 and violacein prompt the nematodes to avoid areas



where pathogenic bacteria are present, thereby enhancing their survival.<sup>91</sup> 1-undecene, a volatile compound derived from *Pseudomonas aeruginosa*, acts as a pathogen-associated molecular pattern that mediates aversive response in *C. elegans*. Additionally, the metabolite induces immune effectors specific to *P. aeruginosa* via the AWB olfactory neurons, suggesting dual functions of microbial metabolites in host defense.<sup>92</sup>

In contrast to mediating avoidance, some microbial metabolites act as attractants. Yeast-produced volatiles including ethanol, 1-propanol, acetic acid, ethyl acetate, ethyl hexanoate and 1-butanol, have been shown to attract tephritids and drosophilid flies.<sup>93,94</sup> These compounds signal the presence of fermenting fruits, which are optimal sites for feeding and oviposition. In the oriental fruit fly *Bactrocera dorsalis*, the gut bacterium *Citrobacter* sp. produces 3-hexenyl acetate. This volatile compound serves as an oviposition attractant, guiding female fruit flies to fruits harboring the bacterium.<sup>95</sup> In the red turpentine beetle *Dendroctonus valens*, the frass microbiome produces verbenone, which is higher in females and serves as a pheromone to attract males and thus coordinated attacks on pine trees.<sup>96,97</sup> For bumble bees (*Bombus impatiens*), nectar-inhabiting bacterium *Asaia astilbes* and fungus *Metschnikowia reukaufii* produce various volatile compounds, such as alcohols, aldehydes, esters, isoprenoids and ketones, among which the bee shows a strong olfactory preference for 2-ethyl-1-hexanol that is highly produced by the bacterium. Interestingly, bees consumed more *Metschnikowia*-conditioned nectar than *Asaia*-conditioned nectar, suggesting the microbial metabolites elicit distinct olfactory and gustatory preferences.<sup>98</sup> SCFAs produced by microbes are also known ligands of olfactory receptors<sup>70</sup>. For instance, propionic acid can elicit opposing behaviors in closely related species, attracting *D. melanogaster* larvae while repelling *D. suzukii* larvae.<sup>99</sup>

While these examples illustrate the roles of individual microbes, interactions between microbial species can give rise to new metabolites that modulate olfactory behavior in unique ways. For instance, *D. melanogaster* prefers co-cultures of *Saccharomyces* and *Acetobacter* over the same species grown separately. This olfactory preference is driven by acetate and related volatiles produced when *Acetobacter* metabolizes ethanol derived

from *Saccharomyces*. Such emergent properties of microbial community interactions, driven by metabolic exchanges,<sup>7</sup> provide fascinating insights into how multi-species microbiomes influence olfactory behavior.

In summary, both intrinsic and external cues from microbial metabolite are important drivers of olfactory behavior. Microbial metabolites affect not only the structure of olfactory tissues but also modulate how animals perceive and respond to odors. Additionally, microbial volatile signals can function as semiochemicals driving behavioral variation in response to a changing environment. Outstanding questions remain regarding the role of microbiomes in different body compartments, whether in the gut, nasal cavity, or other tissues, in modulating olfactory behaviors. The potential of multi-species microbial interactions in generating novel chemicals that modulate olfactory responses also warrants further investigation.

### Circadian rhythms

Circadian rhythms represent one of the most finely orchestrated biobehavioral systems, governing the temporal organization of various physiological and behavioral processes, from sleep to cognitive functions and metabolic activities. These rhythms are synchronized with the 24-h light-dark cycle and are regulated by a network of a central clock in the brain and peripheral clocks in other tissues.<sup>100,101</sup> While these clocks were traditionally thought to be influenced by genetic and environmental factors, recent research reveals the gut microbiome's role in modulating circadian processes.<sup>101–106</sup> Chronotypes, which describes variations in individual circadian expressions such as “morning”, “evening” and “neither” chronotypes,<sup>107</sup> are emergent properties of the complex interactions involving the microbiome, diet, and the circadian system.<sup>106</sup>

Despite not being directly exposed to light, the gut microbiome demonstrates diurnal oscillations in both its composition and function. A study in mice found that about 60% of gut microbial species show rhythmic fluctuations, with certain microbial pathways involved in energy metabolism, DNA repair, and cell growth peaking during the dark phase, while others involved in detoxification,



motility, and environmental sensing are more active during the light phase.<sup>108</sup> Interestingly, microbial oscillations are tightly linked to the hosts' circadian rhythms. For instance, mice with mutations in core clock genes exhibited significant microbial community shifts coupled with the loss of rhythms in specific microbial taxa.<sup>109</sup> While the exact mechanisms linking microbial rhythms and host circadian processes remain to be fully established, emerging evidence suggests that microbial metabolites are key mediators in this interaction.

Microbial SCFAs have been shown to modulate the entrainment of peripheral clock genes within tissues such as the liver and kidney in mice.<sup>110</sup> The timing of SCFA exposure is crucial for the effect, signifying that the microbiome communicates with host tissues to synchronize peripheral clocks. Using mice intestinal epithelial organoids,<sup>111</sup> demonstrated that specific microbial SCFAs induced circadian phase shifts in a concentration-dependent manner. The effect appears to involve histone deacetylase (HDAC) inhibition, implicating microbial metabolites in the modulation of host epigenetics as a novel mechanism for circadian rhythm regulation. In humans, a study examining the relationship among circadian rhythms, eating behavior, and gut microbes showed that microbial SCFA (acetate, propionate, and butyrate) levels decreased as the day progressed. These changes were associated with time-dependent shifts in microbial compositions influenced by eating behaviors such as meal timing and frequency.<sup>112</sup> Moreover, butyrate supplementation was shown to upregulate circadian-clock genes (CRY1, CRY2, PER1, and BMAL1) and improve sleep quality in ulcerative colitis patients, highlighting its potential as an adjunct therapy for mitigating disease symptoms.<sup>113</sup>

In addition to SCFAs, the microbiome also regulates circadian rhythms through the production of other metabolites, such as polyamines and bile acids. Polyamines can influence the interactions between clock proteins.<sup>114</sup> Perturbation in polyamine levels, such as feeding on a diet low in polyamines or antibiotic treatment, lead to changes in the hepatic circadian transcriptome in mice.<sup>105</sup> Certain bacteria and fungi can produce melatonin, a hormone recognized for regulating sleep-wake cycles. Emerging evidence suggests that the gut microbiome may influence circadian rhythm

through melatonin synthesis and metabolism, positioning it as a potential therapeutic target for dysbiosis and circadian rhythm disorders.<sup>115</sup>

Diet has long been recognized to influence circadian rhythms. For example, high-fat diets can disrupt circadian clock timing and alter the expression of key circadian genes.<sup>116,117</sup> A review by<sup>118</sup> highlights examples in which different dietary conditions (high/low fats, sugars, fibers) modulate the gut microbiome composition, which in turn affect circadian rhythms, supporting the role of gut microbiome as a transducer of dietary signals to regulate both circadian rhythms and metabolism. In this context,<sup>119</sup> showed that microbial metabolism of bile acids impacts circadian rhythms. Specifically, they generated a mutant strain of *Bacteroides thetaiotaomicron* lacking the bile salt hydrolase (BSH) enzyme and colonized germ-free mice with either the mutant or wild-type strain. Mice colonized with the BSH-deficient bacteria had higher bile acid levels, gained less weight on a high-fat diet, and exhibited lower fat levels in blood and liver compared to those with the wild-type strain. These mice also exhibited a metabolic shift, favoring burning fat over carbohydrate for energy. The altered metabolism was coupled with differential expression of circadian rhythm genes in the distal ileum. Furthermore, unconjugated bile acids produced through microbial deconjugation of liver-secreted bile acids, such as deoxycholic acid and chenodeoxycholic acid, have been shown to increase the amplitude of clock genes including PER and CRY genes.<sup>120</sup> The effects have been observed across multiple mouse tissues, including the ileum, colon, and liver. These findings suggest bile acids may act as chronobiological regulators, linking dietary inputs to circadian control.

In summary, although gut microbes do not directly perceive light, their composition and metabolic activities exhibit diurnal rhythms that not only synchronize with, but also modulate host circadian rhythms. Various microbial metabolites, including SCFAs, polyamines, bile acids, and melatonin, can act as biochemical mediators influencing circadian genes' expressions, the entrainment of peripheral clocks, and circadian-related behavioral outputs such as sleep. These findings emphasize the microbiome's role as an integral component of circadian regulatory systems.



## Locomotion

Locomotion is a highly coordinated process that integrates neural, motor, and metabolic systems, serving as the foundation for all other behaviors discussed in this review. Decline in locomotor function is a hallmark of aging, while abnormalities in locomotor behavior are prominent symptoms in a range of neurological diseases, such as Parkinson's and Alzheimer's diseases. The microbiome has been implicated in influencing locomotion across various animal models.<sup>121–125</sup> Though outcomes can vary depending on factors such as age, sex, and genetic background, research has begun to unravel specific microbial effectors and metabolites involved in modulating locomotion.

For example, maternal exposure to bacterial endotoxin lipopolysaccharide (LPS) during late pregnancy significantly alters locomotive response in rat offspring.<sup>126</sup> Specifically, adult offspring from LPS-treated dams exhibited increased amphetamine (AMPH)-induced locomotion compared to those from saline-treated dams. This observation raises the possibility that prenatal exposure to bacterial endotoxins sensitize the dopaminergic system, as AMPH acts on dopamine signaling by promoting the release of dopamine and blocking its reuptake through inhibiting the dopamine transporter. In addition, germ-free mice administered with live *Lactobacillus plantarum* showed increased locomotor behavior associated with increased dopamine and serotonin levels in the striatum.<sup>127</sup> These findings point to microbial interactions with neurotransmitter pathways as a potential mechanism underlying locomotion. Microbial modulation of host locomotion can also be mediated through gut hormone signaling.<sup>125</sup> shows that mice treated with a broad-spectrum antibiotic cocktail exhibited reduced locomotor activity, associated with elevated levels of the gut hormone GLP-1. The reduced locomotion could be reversed by blocking the GLP-1 receptor or disrupting vagal signaling. Importantly, when germ-free mice were re-colonized with *Lactobacillus reuteri* and *Bacteroides thetaiotaomicron*, GLP-1 levels were suppressed, and normal locomotor activity was restored, demonstrating that these specific gut microbes regulate locomotion through GLP-1 signaling and vagal pathways.

Several metabolic cues or mechanisms underlying microbial effects on locomotion have been identified. In female *D. melanogaster*, the gut bacterium *Lactobacillus brevis* was shown to influence locomotive behavior through modulating host sugar levels with the bacterial enzyme xylose isomerase.<sup>122</sup> The study further pinpointed octopamine as a key player by showing that thermogenetic activation of octopaminergic neurons or administering octopamine suppressed the locomotion-modulating effects of xylose isomerase.

In *C. elegans*, feeding with the breast milk-derived *Lacticaseibacillus rhamnosus* has been shown to enhance locomotion and slow the decline in muscle function, while also significantly extending lifespan. The effect is associated with increased levels of specific bacterial metabolites, including sphingolipids, galactose, amino acids and fatty acids, and involves central stress-response (p38 MAPK) and insulin (daf-2) pathways.<sup>128</sup>

The locomotion-stimulating effects of microbial-derived propionic acid have also been shown in rats.<sup>129</sup> demonstrated that intraventricular infusions of propionic acid significantly increased locomotion associated with neuroinflammation and oxidative stress in specific brain regions.<sup>130</sup> showed that systemic administration of propionic acid at high concentrations led to conditioned taste and place avoidance in rats, indicating that this metabolite not only stimulates locomotion but also induces aversive behavioral responses. Conversely rats injected with a high dose of microbially-produced indole traveled shorter distance compared to control rats.<sup>131</sup> Collectively, these examples illustrate how microbial metabolites can exert both stimulatory and inhibitory effects on locomotion, and how microbial metabolism can influence systemic metabolic states, which in turn affect behavior.

The relevance of microbial effects on locomotion and neurological disorders is suggested by a study by.<sup>124</sup> In this study, mice transplanted with fecal microbiome from schizophrenia patients displayed schizophrenia-like behaviors, including hyper locomotion and impaired learning and memory. These behavioral changes were accompanied by disruptions in the kynurenine pathway linked to tryptophan metabolism. Specifically, the transplanted mice showed elevated levels of



kynurenic acid, a metabolite that acts as an antagonist to N-methyl-D-aspartate (NMDA) receptors, potentially contributing to the observed behavioral abnormalities. This study raised the question of whether neurological disorders like schizophrenia may be transmissible through the microbiome and whether microbiome intervention can be applied to treat the disorder.

The therapeutic potentials of microbial compounds and metabolites in managing locomotion disorders have also been a subject of growing interest. Combined LPS and the anti-inflammatory drug indomethacin treatment was shown to significantly improve cellular repair and locomotor function in rats with spinal cord injury.<sup>132</sup> Germ-free mice administered with microbial amino acids, SCFAs, and bile acids also showed an increase in skeletal muscle mass and improved muscle strength involved in locomotion, compared to untreated counterparts,<sup>121,133</sup> pointing to microbial metabolites as potential therapeutic agents managing conditions like Duchenne muscular dystrophy.<sup>133</sup>

With accumulating evidence demonstrating that microbial metabolites such as SCFAs, indoles, sphingolipids, and amino acids can influence locomotion, current literature also highlights how factors like early-life exposure, antibiotic treatment, and fecal transplantation, can alter locomotor behavior by reshaping the microbiomes. These findings have important implications for understanding and potentially treating motor and neurological disorders. One striking aspect is that the same metabolites can elicit stimulating or inhibiting effects depending on the species or context. More work is needed to unravel the underlying mechanisms driving these divergent outcomes and behavioral variability.

## Reproductive behavior

Both the gut microbiome and microbiomes associated with reproductive organs (referred to as the “reproductive microbiome”) have been shown to affect reproductive physiology and behavior, including mating and sexual selection.<sup>38,134–142</sup> While microbial influence on reproductive behavior is increasingly recognized, the underlying mechanisms are not yet fully understood.<sup>136,143,144</sup> Recent studies have begun to elucidate the impact

of microbial metabolites on reproductive health and behavior. For instance, the fungal metabolite zearalenone produced by *Fusarium* in animal feeds has been shown to promote reproductive organ growth in pigs, increasing the weight of reproductive tracts and sizes of the uterine and vulvar areas.<sup>145</sup> In *Trichuris* nematodes, reduced levels of microbial-derived arginine were associated with decreased reproductive capacity.<sup>146</sup> In giant pandas, metabolites such as acetic acid and 1-hexanol alcohols produced by gut bacteria *Veillonellaceae* and *Lactobacillaceae* are speculated to serve as precursors for the synthesis of sex pheromones in the perianal glands, influencing mate selection and mating behavior.<sup>147</sup>

In *C. elegans*, the fungal metabolite 2,5-diketopiperazine gliotoxin, produced by *Penicillium*, *Myrothecium*, and *Aspergillus*, induce egg-laying behavior by targeting the serotonin receptors.<sup>148</sup> The synergistic production of lactate and isoleucine by the *Drosophila* gut microbes *Acetobacter pomorum* and *Lactobacillus plantarum* increased female oviposition.<sup>8</sup> Also, production of lactate by *Enterococcus* ameliorated the negative effect alkaline environment had on the ovipositional choices of *Drosophila*.<sup>149</sup> The importance of microbiome on sex-specific reproductive behavior is further illustrated by studies on *D. suzukii*, where axenic female flies show reduced foraging activity and oviposition compared to conventionally reared flies.<sup>150</sup> The behavioral effect is likely associated with the lack of bacterial-derived vitamin B2 that is crucial for oogenesis in flies.<sup>150,151</sup>

Taken together, studies in model organisms consistently show that axenic hosts show declined reproductive capacity, highlighting the microbiome’s role in reproductive fitness. Microbial metabolites can influence host reproductive behavior through multiple routes, by promoting the growth of reproductive organs, serving as sexual pheromones, and impacting the pathways governing mating and oviposition behaviors.

## Aggression

Studies on animal models including *Drosophila*, mice,<sup>152–154</sup> and chicken,<sup>155–157</sup> have provided valuable insights into the role of microbiome in modulating aggressive behaviors. They have



revealed that the presence or absence of the microbiome can lead to notable differences in aggressiveness. For example, in *Drosophila*, axenic males displayed reduced aggressive behaviors, such as fewer lunging attacks and prolonged fighting latency, compared to their conventionally raised counterparts. Axenic female flies also showed a decrease in head-butting frequency and took longer to initiate such aggressive actions when competing for resources like yeast food. These behavioral differences were linked to alterations in octopamine levels.<sup>153</sup> Infection with *Wolbachia* has been shown to reduce aggressive behavior in *Drosophila* males, which is also associated with reduced octopamine levels.<sup>158</sup>

In pigs, tail-biting behavior, a form of aggression where pigs bite the tail of other and cause injuries, is more prevalent in individuals with a higher relative abundance of Firmicutes in their gut microbiome. These “biter” pigs also had lower levels of fecal SCFAs such as acetate, propionate, butyrate and valerate, but higher plasma SCFAs levels.<sup>159</sup> Similarly, in chickens, dominant roosters that engaged in aggressive behaviors such as pecking or scratching other birds, had higher levels of microbial SCFAs, including acetic acid, propionic acid, butyric acid, and valerate acid than in less dominant roosters.<sup>155</sup> Total microbial SCFAs and lactates were also found to be higher in the cecum of hens exhibiting high feather-pecking behavior than those with low feather-pecking behavior, whereas the levels of biogenic amines such as putrescine and cadaverine were inversely associated with the feather-pecking behavior.<sup>160</sup> In rats, subcutaneous administration of propionic acid has been shown to induce stronger aggressive behavior 14 days post-administration.<sup>161</sup> While the above examples suggest a positive association between microbial SCFA and various aggressive behaviors, interestingly, in humans, the levels of microbially-produced SCFAs were shown to be reduced in schizophrenia patients displaying aggressive behaviors.<sup>162</sup>

Another mechanism involved in modulating aggression behavior is nitrogen metabolism. Gut bacteria in rats and humans, such as *Escherichia coli* and *Lactobacillus*, have shown the capacity to produce nitric oxide (NO) from nitrate or nitrite<sup>163,164</sup> and NO is involved in the display of

aggressive behavior, particularly in male mice, through interactions with serotonin.<sup>165</sup>

To conclude, aggression often arises as a result of direct competition with others or in response to threats. This makes aggression behavior sensitive to acute environmental cues. It is inherently social, context-dependent, and variable even within a species. Microbial metabolites like SCFAs, nitric oxide, and biogenic amines can alter the expression of aggression, sometimes in contradictory ways. In some species, for example, SCFAs can promote aggression, whereas they are linked to reduced aggression or social withdrawal in others. Such variability underscores the context-dependent nature of the microbiome in modulating aggression.

## Social behavior

The relationship between the microbiome and social behavior is reciprocal. Social behavior can influence microbial exposure and acquisition, whereas the microbiome has been implicated in social behavior regulation.<sup>166–168</sup> An example of microbiome-social behavior connection is implicated in hyenas, where bacterial communities in scent glands, rich in fermentative bacteria, correlate with the volatile fatty acid in their scent secretions that are involved in social communication and hierarchical structure.<sup>169</sup> However, a subsequent study indicate that social rank does not predict microbiome composition in hyena, though there are notable sex differences in the anal scent glands of juvenile hyenas and age-related differences in the prepuce and rectal microbiome between juveniles and adults.<sup>170</sup> In wild Verreaux's sifaka lemurs (*Propithecus verreauxi*), social group membership is reflected in the microbiomes of individual. Groups with denser grooming networks have more homogeneous gut microbial compositions, while more gregarious adult individuals and those that scent-mark frequently have greater microbial diversity.<sup>171</sup>

Further supporting the link between microbiome and social behavior, recent studies have shown that gut-derived metabolites can impact social behaviors in various animals. For example, administration of ergothioneine, a metabolite produced by the gut bacterium *Lactobacillus reuteri*, reduced social avoidance behavior in rats.<sup>172</sup>



Injection of the SCFAs, including acetate, butyrate and propionate into the brains of germ-free male mice, resulted in a decrease in the display of social novelty (described as time expended to recognize a new conspecific female mouse) compared to controls injected with artificial cerebrospinal fluid.<sup>173</sup> In addition to its role in olfaction mentioned earlier, trimethylamine N-oxide (TMAO) administered to mice resulted in lowered social dominance and reduced sexual preference, associated with significant changes in abundance over 200 metabolites.<sup>174</sup>

Research has also linked microbial metabolites to social behaviors in the context of developmental disorders. For instance, an assessment of fecal metabolites from infants found an association between variations in the levels of microbial metabolites, especially higher lactate and lower SCFAs levels, and fewer autism-related behaviors, depicted by a lower score on the social responsiveness scale (a rating scale used to measure behaviors related to autism spectrum disorder (ASD), where higher scores show more ASD-related behavior).<sup>175</sup>

The impact of social environments on the microbiome and behavior has also been explored. Juvenile social isolation in mice was found to increase the level of propionic acid in the gut. Mice reconstituted with fecal microbiome from socially-isolated mice or grouped-house mice supplemented with propionic acid all exhibited anxiety behavior and social deficits, mirroring the effects of juvenile social isolation.<sup>176</sup> Transplantation of specific gut bacteria *Clostridiales*, *Lachnospiraceae* and *Ruminococcaceae* to germ-free mice also induced social avoidance behavior in the recipient mice and the effect was associated with high production of the microbial metabolite, cresol.<sup>177</sup> A study on wild pandas showed that the microbial composition of the pandas' feces and scent marking sites showed varied correlation with various volatile compounds, including heptadecane, L- $\alpha$ -terpineol, nonanal, iso-isovelleral, decanal and metabolites such as 11 $\beta$ -hydroxyandrosterone, idebenone, glycerol-3-phosphate that were also found in pandas' scent marks.<sup>178</sup> Although the precise roles of these individual compounds in modulating social interactions have not been tested, they appear to be signatures of the pandas' scent marks that function as cues for kin recognition and sex identification.<sup>179,180</sup> In insects, metabolites directly produced by the

microbiome or which production is mediated by the microbiome, such as cuticular hydrocarbons (CHC), function as aggregation pheromones or kin recognition signals.<sup>181</sup> For instance, antibiotic treatment in leaf-cutting ants altered their microbial composition and CHC profiles, leading to the ants receiving higher attacks from nestmates.<sup>182</sup> Similarly, in the termite, *Reticulitermes speratus*, members covered in different bacterial odors from another colony faced heightened aggression from nestmates.<sup>183</sup>

In summary, studies have highlighted the dynamic feedback loop between the microbiome and social behavior, where the microbiome both modulates social interactions and is shaped by the social environments of the individuals. Microbial metabolites such as SCFAs, ergothioneine, cresol, and cuticular hydrocarbons have been identified as drivers of kin recognition and hierarchical interactions within populations. More research is needed to elucidate the mechanisms underlying how microbial metabolites regulate social behavior and the extent to which social environments influence the microbiome composition during development and across lifespan.

## Conclusion and future directions

The microbiome's influence on animal behavior through specialized microbial metabolites is increasingly recognized. These metabolites are engines of behavioral variation, helping hosts adapt to changing environments, but dysregulation can lead to aberrant behaviors and diseases. Despite recent advances, significant gaps remain in our understanding of the underlying mechanisms. Here, we highlighted several topics for future research.

- (1) A comprehensive understanding of the host receptors and pathways that interact with microbial metabolites is foundational for advancing this field.<sup>184</sup> While several receptors, such as G protein-coupled receptors (GPCRs),<sup>65,185,186</sup> aryl hydrocarbon receptor,<sup>187,188</sup> pregnane X receptor,<sup>189,190</sup> IL-10 receptor<sup>191</sup> and peroxisome proliferator-activated receptor  $\gamma$ ,<sup>192</sup> have been linked to microbial modulation of host behaviors, many are yet to be discovered. A deeper



understanding of these receptors and their associated pathways is crucial to advancing our comprehension of the microbiome's impact on behavior.

- (2) The role of epigenetic mechanisms in mediating microbiome-induced behavioral changes. Epigenetic mechanisms such as DNA methylation, chromatin modeling, histone modification, and noncoding RNA are emerging as modulators of neuroplasticity and behavior.<sup>193–195</sup> For instance, *Drosophila* exposed to a high-sugar diet showed transgenerational reduced sweet sensitivity. The effect is attributed to upregulation of histone methylation, H3K27me3, transmitted maternally.<sup>196</sup> Also, in *C. elegans*, maternal exposure to pathogenic *Pseudomonas aeruginosa* resulted in progeny that avoided the pathogen, a behavior modulated by RNA-mediated regulation of gene expression.<sup>197</sup> Microbial metabolites such as SCFAs function as modulators of the host epigenetic process.<sup>198–203</sup> Microbiome-mediated choline metabolism has also been shown to affect DNA methylation and anxiety behavior in mice.<sup>204</sup> Given the central role of epigenetics in behavioral plasticity, elucidating how the microbiome influences epigenetic pathways in behavioral modulation represents a major advancement in the field.
- (3) Unlocking the potential of biosynthetic clusters. The vast diversity of the microbiome and its untapped biosynthetic pathways present both challenges and opportunities for future research. Many microbial biosynthetic clusters are inactive under standard laboratory conditions, which limits our ability to assess their full biological potentials.<sup>5</sup> Efforts to optimize and engineer microbial communities to activate these latent pathways could unlock a broader array of microbial metabolites that can modulate host behaviors. This would not only expand our knowledge of microbial contribution to behavioral variation but also offer opportunities to harness these metabolites as therapeutic agents for behavioral disorders.

## Disclosure statement

No potential conflict of interest was reported by the author(s).

## Funding

We acknowledge funding support from the National Institutes of Health National Institute of General Medical Sciences grant [R35GM147651] and the Florida Agricultural Experiment Station [Hatch project FLA-ENY-006325].

## Data availability statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

## References

1. Demain AL. Importance of microbial natural products and the need to revitalize their discovery. *J Ind Microbiol Biotechnol.* 2014;41(2):185–201. doi: [10.1007/s10295-013-1325-z](https://doi.org/10.1007/s10295-013-1325-z).
2. Van Santen JA, Jacob G, Singh AL, Aniebok V, Balunas MJ, Bunsko D, Neto FC, Castaño-Espriu L, Chang C, Clark TN, et al. The natural products atlas: an open access knowledge base for microbial natural products discovery. *ACS Central Sci.* 2019;5(11):1824–1833. doi: [10.1021/acscentsci.9b00806](https://doi.org/10.1021/acscentsci.9b00806).
3. van Santen JA, Poynton EF, Iskakova D, McMann E, Alsup T, Clark TN, Fergusson CH, Fewer DP, Hughes AH, McCadden CA, et al. The natural products atlas 2.0: a database of microbially-derived natural products. *Nucleic Acids Res.* 2022;50(D1):D1317–D1323. doi: [10.1093/nar/gkab941](https://doi.org/10.1093/nar/gkab941).
4. Brakhage AA, Schroeckh V. Fungal secondary metabolites—strategies to activate silent gene clusters. *Fungal Genet Biol.* 2011;48(1):15–22. doi: [10.1016/j.fgb.2010.04.004](https://doi.org/10.1016/j.fgb.2010.04.004).
5. Rutledge PJ, Challis GL. Discovery of microbial natural products by activation of silent biosynthetic gene clusters. *Nat Rev Microbiol.* 2015;13(8):509–523. doi: [10.1038/nrmicro3496](https://doi.org/10.1038/nrmicro3496).
6. Hoskisson PA, Seipke RF, Wright GD. Cryptic or silent? The known unknowns, unknown knowns, and unknown unknowns of secondary metabolism. *mBio.* 2020;11(5):10–1128. doi: [10.1128/mBio.02642-20](https://doi.org/10.1128/mBio.02642-20).
7. Fischer CN, Trautman EP, Crawford JM, Stabb EV, Handelsman J, Broderick NA. Metabolite exchange between microbiome members produces compounds that influence *Drosophila* behavior. *Elife.* 2017;6:e18855. doi: [10.7554/eLife.18855](https://doi.org/10.7554/eLife.18855).
8. Henriques SF, Dhakan DB, Serra L, Francisco AP, Carvalho-Santos Z, Baltazar C, Elias AP, Anjos M, Zhang T, Maddocks ODK, et al. Metabolic



- cross-feeding in imbalanced diets allows gut microbes to improve reproduction and alter host behaviour. *Nat Commun.* **2020**;11(1):4236. doi: [10.1038/s41467-020-18049-9](https://doi.org/10.1038/s41467-020-18049-9).
9. Huang X, Hu M, Sun T, Li J, Zhou Y, Yan Y, Xuan B, Wang J, Xiong H, Ji L, et al. Multi-kingdom gut microbiota analyses define bacterial-fungal interplay and microbial markers of pan-cancer immunotherapy across cohorts. *Cell Host & Microbe.* **2023**;31(11):1930–1943.e4. doi: [10.1016/j.chom.2023.10.005](https://doi.org/10.1016/j.chom.2023.10.005).
  10. Krautkramer KA, Fan J, Bäckhed F. Gut microbial metabolites as multi-kingdom intermediates. *Nat Rev Microbiol.* **2021**;19(2):77–94. doi: [10.1038/s41579-020-0438-4](https://doi.org/10.1038/s41579-020-0438-4).
  11. Postler TS, Ghosh S. Understanding the holobiont: how microbial metabolites affect human health and shape the immune system. *Cell Metab.* **2017**;26(1):110–130. doi: [10.1016/j.cmet.2017.05.008](https://doi.org/10.1016/j.cmet.2017.05.008).
  12. Salazar N, González S, de Los Reyes Gavilan CG, Rios-Covian D. Branched short-chain fatty acids as biological indicators of microbiota health and links with anthropometry. In: Biomarkers in nutrition. Patel, VB, Preedy, VR (eds). Switzerland: Springer; **2022**. p. 1–17. doi:[10.1007/978-3-030-81304-8\\_4-1](https://doi.org/10.1007/978-3-030-81304-8_4-1).
  13. Qu S, Yu Z, Zhou Y, Wang S, Jia M, Chen T, Zhang X. Gut microbiota modulates neurotransmitter and gut-brain signaling. *Microbiol Res.* **2024**;287:127858. doi: [10.1016/j.micres.2024.127858](https://doi.org/10.1016/j.micres.2024.127858).
  14. Strandwitz P. Neurotransmitter modulation by the gut microbiota. *Brain Res.* **2018**;1693:128–133. doi: [10.1016/j.brainres.2018.03.015](https://doi.org/10.1016/j.brainres.2018.03.015).
  15. Otaru N, Ye K, Mujezinovic D, Berchtold L, Constancias F, Cornejo FA, Krzystek A, de Wouters T, Braegger C, Lacroix C, et al. GABA production by human intestinal *Bacteroides* spp.: prevalence, regulation, and role in acid stress tolerance. *Front Microbiol.* **2021**;12:656895. doi: [10.3389/fmicb.2021.656895](https://doi.org/10.3389/fmicb.2021.656895).
  16. Luck B, Horvath TD, Engevik KA, Ruan W, Haidacher SJ, Hoch KM, Oezguen N, Spinler JK, Haag AM, Versalovic J, et al. Neurotransmitter profiles are altered in the gut and brain of mice mono-associated with *Bifidobacterium dentium*. *Biomolecules.* **2021**;11(8):1091. doi: [10.3390/biom11081091](https://doi.org/10.3390/biom11081091).
  17. Douglas AE. Simple animal models for microbiome research. *Nat Rev Microbiol.* **2019**;17(12):764–775. doi: [10.1038/s41579-019-0242-1](https://doi.org/10.1038/s41579-019-0242-1).
  18. Lemaitre B, Nicolas E, Michaut L, Reichhart JM, Hoffmann JA. The dorsoventral regulatory gene cassette *spätzle/Toll/cactus* controls the potent antifungal response in *Drosophila* adults. *Cell.* **1996**;86(6):973–983. doi: [10.1016/S0092-8674\(00\)80172-5](https://doi.org/10.1016/S0092-8674(00)80172-5).
  19. Lee RC, Feinbaum RL, Ambros V. The *C. elegans* heterochronic gene *lin-4* encodes small RNAs with antisense complementarity to *lin-14*. *Cell.* **1993**;75(5):843–854. doi: [10.1016/0092-8674\(93\)90529-Y](https://doi.org/10.1016/0092-8674(93)90529-Y).
  20. Wightman B, Ha I, Ruvkun G. Posttranscriptional regulation of the heterochronic gene *lin-14* by *lin-4* mediates temporal pattern formation in *C. elegans*. *Cell.* **1993**;75(5):855–862. doi: [10.1016/0092-8674\(93\)90530-4](https://doi.org/10.1016/0092-8674(93)90530-4).
  21. Reddy P, Zehring WA, Wheeler DA, Pirrotta V, Hadfield C, Hall JC, Rosbash M. Molecular analysis of the period locus in *Drosophila melanogaster* and identification of a transcript involved in biological rhythms. *Cell.* **1984**;38(3):701–710. doi: [10.1016/0092-8674\(84\)90265-4](https://doi.org/10.1016/0092-8674(84)90265-4).
  22. Price JL, Blau J, Rothenfluh A, Abodeely M, Kloss B, Young MW. Double-time is a novel *Drosophila* clock gene that regulates PERIOD protein accumulation. *Cell.* **1998**;94(1):83–95. doi: [10.1016/S0092-8674\(00\)81224-6](https://doi.org/10.1016/S0092-8674(00)81224-6).
  23. Csillag A, Ádám Á, Zachar G. Avian models for brain mechanisms underlying altered social behavior in autism. *Front Physiol.* **2022**;13:1032046. doi: [10.3389/fphys.2022.1032046](https://doi.org/10.3389/fphys.2022.1032046).
  24. MaBoudi H, Marshall JAR, Dearden N, Barron AB. How honey bees make fast and accurate decisions. *Elife.* **2023**;12:e86176. doi: [10.7554/eLife.86176](https://doi.org/10.7554/eLife.86176).
  25. Bernays EA. Evolution of feeding behavior in insect herbivores. *Bioscience.* **1998**;48(1):35–44. doi: [10.2307/1313226](https://doi.org/10.2307/1313226).
  26. Ginane C, Bonnet M, Baumont R, Revell DK. Feeding behaviour in ruminants: a consequence of interactions between a reward system and the regulation of metabolic homeostasis. *Anim Production Sci.* **2015**;55(3):247–260. doi: [10.1071/AN14481](https://doi.org/10.1071/AN14481).
  27. Saper CB, Chou TC, Elmquist JK. The need to feed: homeostatic and hedonic control of eating. *Neuron.* **2002**;36(2):199–211. doi: [10.1016/S0896-6273\(02\)00969-8](https://doi.org/10.1016/S0896-6273(02)00969-8).
  28. Schoofs L, De Loof A, Van Hiel MB. Neuropeptides as regulators of behavior in insects. *Annu Rev Entomol.* **2017**;62(1):35–52. doi: [10.1146/annurev-ento-031616-035500](https://doi.org/10.1146/annurev-ento-031616-035500).
  29. Stephens DW, Brown JS, Ydenberg RC. Foraging: behavior and ecology. Chicago, USA: University of Chicago Press; **2007**.
  30. Raubenheimer D, Simpson SJ. Nutritional ecology and foraging theory. *Curr Opin Insect Sci.* **2018**;27:38–45. doi: [10.1016/j.cois.2018.02.002](https://doi.org/10.1016/j.cois.2018.02.002).
  31. Jach ME, Serefko A, Ziaja M, Kieliszek M. Yeast protein as an easily accessible food source. *Metabolites.* **2022**;12(1):63. doi: [10.3390/metabo12010063](https://doi.org/10.3390/metabo12010063).
  32. Graham AE, Ledesma-Amaro R. The microbial food revolution. *Nat Commun.* **2023**;14(1):2231. doi: [10.1038/s41467-023-37891-1](https://doi.org/10.1038/s41467-023-37891-1).
  33. Choi KR, Yu HE, Lee SY. Microbial food: microorganisms repurposed for our food. *Microb Biotechnol.* **2022**;15(1):18–25. doi: [10.1111/1751-7915.13911](https://doi.org/10.1111/1751-7915.13911).
  34. Kim DH, Flavell SW. Host-microbe interactions and the behavior of *Caenorhabditis elegans*. *J Neurogenet.*



- 2020;34(3–4):500–509. doi: [10.1080/01677063.2020.1802724](https://doi.org/10.1080/01677063.2020.1802724).
35. Hoang D, Kopp A, Chandler JA. Interactions between *Drosophila* and its natural yeast symbionts—Is *Saccharomyces cerevisiae* a good model for studying the fly-yeast relationship? *PeerJ*. 2015;3:e1116. doi: [10.7717/peerj.1116](https://doi.org/10.7717/peerj.1116).
  36. Mure A, Sugiura Y, Maeda R, Honda K, Sakurai N, Takahashi Y, Watada M, Katoh T, Gotoh A, Gotoh Y, et al. Identification of key yeast species and microbe–microbe interactions impacting larval growth of *Drosophila* in the wild. *Elife*. 2023;12:RP90148. doi: [10.7554/eLife.90148.3](https://doi.org/10.7554/eLife.90148.3).
  37. Sannino DR, Dobson AJ, Edwards K, Angert ER, Buchon N, McFall-Ngai MJ. The *Drosophila melanogaster* gut microbiota provisions thiamine to its host. *mBio*. 2018;9(2):10–1128. doi: [10.1128/mBio.00155-18](https://doi.org/10.1128/mBio.00155-18).
  38. Wong ACN, Dobson AJ, Douglas AE. Gut microbiota dictates the metabolic response of *Drosophila* to diet. *J Exp Biol*. 2014;217(11):1894–1901. doi: [10.1242/jeb.101725](https://doi.org/10.1242/jeb.101725).
  39. Behar A, Yuval B, Jurkevitch E. Enterobacteria-mediated nitrogen fixation in natural populations of the fruit fly *Ceratitis capitata*. *Mol Ecol*. 2005;14(9):2637–2643. doi: [10.1111/j.1365-294X.2005.02615.x](https://doi.org/10.1111/j.1365-294X.2005.02615.x).
  40. Sabree ZL, Kambhampati S, Moran NA. Nitrogen recycling and nutritional provisioning by *Blattabacterium*, the cockroach endosymbiont. *Proc Natl Acad Sci*. 2009;106(46):19521–19526. doi: [10.1073/pnas.0907504106](https://doi.org/10.1073/pnas.0907504106).
  41. Hu Y, Sanders JG, Łukasik P, D’Amelio CL, Millar JS, Vann DR, Lan Y, Newton JA, Schotanus M, Kronauer DJC, et al. Herbivorous turtle ants obtain essential nutrients from a conserved nitrogen-recycling gut microbiome. *Nat Commun*. 2018;9(1):964. doi: [10.1038/s41467-018-03357-y](https://doi.org/10.1038/s41467-018-03357-y).
  42. Bonakdar M, Czuba LC, Han G, Zhong G, Luong H, Isoherranen N, Vaishnav S. Gut commensals expand vitamin A metabolic capacity of the mammalian host. *Cell Host & Microbe*. 2022;30(8):1084–1092.e5. doi: [10.1016/j.chom.2022.06.011](https://doi.org/10.1016/j.chom.2022.06.011).
  43. Sánchez-Hernández D, Cho CE, Kubant R, Reza-López SA, Poon AN, Wang J, Huot PSP, Smith CE, Anderson GH. Increasing vitamin A in post-weaning diets reduces food intake and body weight and modifies gene expression in brains of male rats born to dams fed a high multivitamin diet. *J Nutritional Biochem*. 2014;25(10):991–996. doi: [10.1016/j.jnutbio.2014.05.002](https://doi.org/10.1016/j.jnutbio.2014.05.002).
  44. Sánchez-Hernández D, Poon AN, Kubant R, Kim H, Huot PSP, Cho CE, Pannia E, Reza-López SA, Pausova Z, Bazinet RP, et al. High vitamin A intake during pregnancy modifies dopaminergic reward system and decreases preference for sucrose in Wistar rat offspring. *J Nutritional Biochem*. 2016;27:104–111. doi: [10.1016/j.jnutbio.2015.08.020](https://doi.org/10.1016/j.jnutbio.2015.08.020).
  45. Ogilvie KM, Saladin R, Nagy TR, Urcan MS, Heyman RA, Leibowitz MD. Activation of the retinoid X receptor suppresses appetite in the rat. *Endocrinology*. 2004;145(2):565–573. doi: [10.1210/en.2003-0907](https://doi.org/10.1210/en.2003-0907).
  46. Magnúsdóttir S, Ravcheev D, de Crécy-Lagard V, Thiele I. Systematic genome assessment of B-vitamin biosynthesis suggests co-operation among gut microbes. *Front Genet*. 2015;6:148. doi: [10.3389/fgene.2015.00148](https://doi.org/10.3389/fgene.2015.00148).
  47. Starke S, Harris DMM, Zimmermann J, Schuchardt S, Oumari M, Frank D, Bang C, Rosenstiel P, Schreiber S, Frey N, et al. Amino acid auxotrophies in human gut bacteria are linked to higher microbiome diversity and long-term stability. *ISME J*. 2023;17(12):2370–2380. doi: [10.1038/s41396-023-01537-3](https://doi.org/10.1038/s41396-023-01537-3).
  48. Coyte KZ, Rakoff-Nahoum S. Understanding competition and cooperation within the mammalian gut microbiome. *Curr Biol*. 2019;29(11):R538–R544. doi: [10.1016/j.cub.2019.04.017](https://doi.org/10.1016/j.cub.2019.04.017).
  49. Culp EJ, Goodman AL. Cross-feeding in the gut microbiome: ecology and mechanisms. *Cell Host & Microbe*. 2023;31(4):485–499. doi: [10.1016/j.chom.2023.03.016](https://doi.org/10.1016/j.chom.2023.03.016).
  50. Wasielewski H, Alcock J, Aktipis A. Resource conflict and cooperation between human host and gut microbiota: implications for nutrition and health. *Ann NY Acad Sci*. 2016;1372(1):20–28. doi: [10.1111/nyas.13118](https://doi.org/10.1111/nyas.13118).
  51. Leitão-Gonçalves R, Carvalho-Santos Z, Francisco AP, Fioreze GT, Anjos M, Baltazar C, Elias AP, Itskov PM, Piper MDW, Ribeiro C, et al. Commensal bacteria and essential amino acids control food choice behavior and reproduction. *PLOS Biol*. 2017;15(4):e2000862. doi: [10.1371/journal.pbio.2000862](https://doi.org/10.1371/journal.pbio.2000862).
  52. Liu Z, Li L, Ma S, Ye J, Zhang H, Li Y, Sair AT, Pan J, Liu X, Li X, et al. High-dietary fiber intake alleviates antenatal obesity-induced postpartum depression: roles of gut microbiota and microbial metabolite short-chain fatty acid involved. *J Agric Food Chem*. 2020;68(47):13697–13710. doi: [10.1021/acs.jafc.0c04290](https://doi.org/10.1021/acs.jafc.0c04290).
  53. Zheng H, Powell JE, Steele MI, Dietrich C, Moran NA. Honeybee gut microbiota promotes host weight gain via bacterial metabolism and hormonal signaling. *Proc Natl Acad Sci*. 2017;114(18):4775–4780. doi: [10.1073/pnas.1701819114](https://doi.org/10.1073/pnas.1701819114).
  54. Igarashi M, Hayakawa T, Tanabe H, Watanabe K, Nishida A, Kimura I. Intestinal GPR119 activation by microbiota-derived metabolites impacts feeding behavior and energy metabolism. *Mol Metab*. 2023;67:101649. doi: [10.1016/j.molmet.2022.101649](https://doi.org/10.1016/j.molmet.2022.101649).
  55. Fu J, Oveisi F, Gaetani S, Lin E, Piomelli D. Oleoylethanolamide, an endogenous PPAR-α agonist, lowers body weight and hyperlipidemia in obese rats. *Neuropharmacology*. 2005;48(8):1147–1153. doi: [10.1016/j.neuropharm.2005.02.013](https://doi.org/10.1016/j.neuropharm.2005.02.013).
  56. Cherbut C, Ferrier L, Rozé C, Anini Y, Blottière H, Lecannu G, Galmiche J-P. Short-chain fatty acids modify colonic motility through nerves and polypeptide YY



- release in the rat. *Am J Physiol-Gastr L.* **1998**;275(6):G1415–G1422. doi: [10.1152/ajpgi.1998.275.6.G1415](https://doi.org/10.1152/ajpgi.1998.275.6.G1415).
57. Psichas A, Sleeth ML, Murphy KG, Brooks L, Bewick GA, Hanyaloglu AC, Ghatei MA, Bloom SR, Frost G. The short chain fatty acid propionate stimulates GLP-1 and PYY secretion via free fatty acid receptor 2 in rodents. *Int J Obes.* **2015**;39(3):424–429. doi: [10.1038/ijo.2014.153](https://doi.org/10.1038/ijo.2014.153).
  58. Christiansen CB, Gabe MBN, Svendsen B, Dragsted LO, Rosenkilde MM, Holst JJ. The impact of short-chain fatty acids on GLP-1 and PYY secretion from the isolated perfused rat colon. *Am J Physiol-Gastr L.* **2018**;315(1):G53–G65. doi: [10.1152/ajpgi.00346.2017](https://doi.org/10.1152/ajpgi.00346.2017).
  59. Zhang Y, Li X, Huang G, Wang H, Chen H, Su Y, Yu K, Zhu W. Propionate stimulates the secretion of satiety hormones and reduces acute appetite in a cecal fistula pig model. *Anim Nutr.* **2022**;10:390–398. doi: [10.1016/j.aninu.2022.06.003](https://doi.org/10.1016/j.aninu.2022.06.003).
  60. Chimere C, Emery E, Summers DK, Keyser U, Gribble FM, Reimann F. Bacterial metabolite indole modulates incretin secretion from intestinal enteroendocrine L cells. *Cell Rep.* **2014**;9(4):1202–1208. doi: [10.1016/j.celrep.2014.10.032](https://doi.org/10.1016/j.celrep.2014.10.032).
  61. Roager HM, Licht TR. Microbial tryptophan catabolites in health and disease. *Nat Commun.* **2018**;9(1):3294. doi: [10.1038/s41467-018-05470-4](https://doi.org/10.1038/s41467-018-05470-4).
  62. Wang Q, Lin H, Shen C, Zhang M, Wang X, Yuan M, Yuan M, Jia S, Cao Z, Wu C, et al. Gut microbiota regulates postprandial GLP-1 response via ileal bile acid-TGR5 signaling. *Gut Microbes.* **2023**;15(2):2274124. doi: [10.1080/19490976.2023.2274124](https://doi.org/10.1080/19490976.2023.2274124).
  63. Reigstad CS, Salmonson CE, Rainey JF III, Szurszewski JH, Linden DR, Sonnenburg JL, Farrugia G, Kashyap PC. Gut microbes promote colonic serotonin production through an effect of short-chain fatty acids on enterochromaffin cells. *FASEB J.* **2015**;29(4):1395. doi: [10.1096/fj.14-259598](https://doi.org/10.1096/fj.14-259598).
  64. Vincent AD, Wang XY, Parsons SP, Khan WI, Huizinga JD. Abnormal absorptive colonic motor activity in germ-free mice is rectified by butyrate, an effect possibly mediated by mucosal serotonin. *Am J Physiol-Gastr L.* **2018**;315(5):G896–G907. doi: [10.1152/ajpgi.00237.2017](https://doi.org/10.1152/ajpgi.00237.2017).
  65. Cook TM, Gavini CK, Jesse J, Aubert G, Gornick E, Bonomo R, Gautron L, Layden BT, Mansuy-Aubert V. Vagal neuron expression of the microbiota-derived metabolite receptor, free fatty acid receptor (FFAR3), is necessary for normal feeding behavior. *Mol Metab.* **2021**;54:101350. doi: [10.1016/j.molmet.2021.101350](https://doi.org/10.1016/j.molmet.2021.101350).
  66. Xiong Y, Miyamoto N, Shibata K, Valasek MA, Motoike T, Kedzierski RM, Yanagisawa M. Short-chain fatty acids stimulate leptin production in adipocytes through the G protein-coupled receptor GPR41. *Proc Natl Acad Sci.* **2004**;101(4):1045–1050. doi: [10.1073/pnas.2637002100](https://doi.org/10.1073/pnas.2637002100).
  67. Fetissov SO. Role of the gut microbiota in host appetite control: bacterial growth to animal feeding behaviour. *Nat Rev Endocrinol.* **2017**;13(1):11–25. doi: [10.1038/nrendo.2016.150](https://doi.org/10.1038/nrendo.2016.150).
  68. Wachsmuth HR, Weninger SN, Duca FA. Role of the gut–brain axis in energy and glucose metabolism. *Exp Mol Med.* **2022**;54(4):377–392. doi: [10.1038/s12276-021-00677-w](https://doi.org/10.1038/s12276-021-00677-w).
  69. Ridlon JM, Kang DJ, Hylemon PB, Bajaj JS. Bile acids and the gut microbiome. *Curr Opin In Gastroenterol.* **2014**;30(3):332–338. doi: [10.1097/MOG.000000000000057](https://doi.org/10.1097/MOG.000000000000057).
  70. Raybould HE, Zumpano DL. Microbial metabolites and the vagal afferent pathway in the control of food intake. *Physiol Behav.* **2021**;240:113555. doi: [10.1016/j.physbeh.2021.113555](https://doi.org/10.1016/j.physbeh.2021.113555).
  71. Goswami C, Iwasaki Y, Yada T. Short-chain fatty acids suppress food intake by activating vagal afferent neurons. *J Nutritional Biochem.* **2018**;57:130–135. doi: [10.1016/j.jnutbio.2018.03.009](https://doi.org/10.1016/j.jnutbio.2018.03.009).
  72. Irazoki O, Hernandez SB, Cava F. Peptidoglycan muropeptides: release, perception, and functions as signaling molecules. *Front Microbiol.* **2019**;10:10. doi: [10.3389/fmicb.2019.00500](https://doi.org/10.3389/fmicb.2019.00500).
  73. Gabanyi I, Lepousez G, Wheeler R, Vieites-Prado A, Nissant A, Chevalier G, Wagner S, Moigneu C, Dulauroy S, Hicham S, et al. Bacterial sensing via neuronal Nod2 regulates appetite and body temperature. *Science.* **2023**;376(6590):eabj3986. doi: [10.1126/science.abj3986](https://doi.org/10.1126/science.abj3986).
  74. Bear DM, Lassance JM, Hoekstra HE, Datta SR. The evolving neural and genetic architecture of vertebrate olfaction. *Curr Biol.* **2016**;26(20):R1039–R1049. doi: [10.1016/j.cub.2016.09.011](https://doi.org/10.1016/j.cub.2016.09.011).
  75. Kannan K, Galizia CG, Nouvian M. Olfactory strategies in the defensive behaviour of insects. *Insects.* **2022**;13(5):470. doi: [10.3390/insects13050470](https://doi.org/10.3390/insects13050470).
  76. Keesey IW, Hansson BS. Neuroecology of alcohol preference in *Drosophila*. *Annu Rev Entomol.* **2022**;67(1):261–279. doi: [10.1146/annurev-ento-070721-091828](https://doi.org/10.1146/annurev-ento-070721-091828).
  77. Schild SLA, Rørvang MV. Pig olfaction: the potential impact and use of odors in commercial pig husbandry. *Front Anim Sci.* **2023**;4:1215206. doi: [10.3389/fanim.2023.1215206](https://doi.org/10.3389/fanim.2023.1215206).
  78. Derby CD, Caprio J. What are olfaction and gustation, and do all animals have them? *Chem Senses.* **2024**;49:bjae009. doi: [10.1093/chemse/bjae009](https://doi.org/10.1093/chemse/bjae009).
  79. Maraci Ö, Engel K, Caspers BA. Olfactory communication via microbiota: what is known in birds? *Genes (Basel).* **2018**;9(8):387. doi: [10.3390/genes9080387](https://doi.org/10.3390/genes9080387).
  80. Bienenstock J, Kunze WA, Forsythe P. Disruptive physiology: olfaction and the microbiome–gut–brain axis. *Biol Rev.* **2018**;93(1):390–403. doi: [10.1111/brev.12348](https://doi.org/10.1111/brev.12348).
  81. Qiao H, Keesey IW, Hansson BS, Knaden M. Gut microbiota affects development and olfactory behavior in *drosophila melanogaster*. *J Exp Biol.* **2019**;222(5):jeb192500. doi: [10.1242/jeb.192500](https://doi.org/10.1242/jeb.192500).



82. Yan M, Pamp SJ, Fukuyama J, Hwang P, Cho D-Y, Holmes S, Relman D. Nasal microenvironments and interspecific interactions influence nasal microbiota complexity and *S. aureus* carriage. *Cell Host & Microbe*. 2013;14(6):631–640. doi: [10.1016/j.chom.2013.11.005](https://doi.org/10.1016/j.chom.2013.11.005).
83. François A, Grebert D, Rhimi M, Mariadassou M, Naudon L, Rabot S, Meunier N. Olfactory epithelium changes in germfree mice. *Sci Rep*. 2016;6(1):24687. doi: [10.1038/srep24687](https://doi.org/10.1038/srep24687).
84. Massey W, Kay KE, Jaramillo TC, Horak AJ, Cao S, Osborn LJ, Banerjee R, Mrdjen M, Hamoudi MK, Silver DJ, et al. Metaorganismal choline metabolism shapes olfactory perception. *J Biol Chem*. 2023;299(11):105299. doi: [10.1016/j.jbc.2023.105299](https://doi.org/10.1016/j.jbc.2023.105299).
85. Zhang Z, Mu X, Cao Q, Shi Y, Hu X, Zheng H. Honeybee gut *Lactobacillus* modulates host learning and memory behaviors via regulating tryptophan metabolism. *Nat Commun*. 2022;13(1):2037. doi: [10.1038/s41467-022-29760-0](https://doi.org/10.1038/s41467-022-29760-0).
86. Wong ACN, Wang QP, Morimoto J, Senior AM, Lihoreau M, Neely GG, Simpson SJ, Ponton F. Gut microbiota modifies olfactory-guided microbial preferences and foraging decisions in *Drosophila*. *Curr Biol*. 2017;27(15):2397–2404.e4. doi: [10.1016/j.cub.2017.07.022](https://doi.org/10.1016/j.cub.2017.07.022).
87. Farine JP, Habbachi W, Cortot J, Roche S, Ferveur JF. Maternally-transmitted microbiota affects odor emission and preference in *Drosophila* larva. *Sci Rep*. 2017;7(1):6062. doi: [10.1038/s41598-017-04922-z](https://doi.org/10.1038/s41598-017-04922-z).
88. Aziz RA, Ramesh P, Suchithra KV, Stothard P, Narayana VK, Raghu SV, Shen F-T, Young C-C, Prasad TSK, Hameed A. Comprehensive insights into the impact of bacterial indole-3-acetic acid on sensory preferences in *drosophila melanogaster*. *Sci Rep*. 2024;14(1):14. doi: [10.1038/s41598-024-58829-7](https://doi.org/10.1038/s41598-024-58829-7).
89. O'Donnell MP, Fox BW, Chao PH, Schroeder FC, Sengupta P. A neurotransmitter produced by gut bacteria modulates host sensory behaviour. *Nature*. 2020;583(7816):415–420. doi: [10.1038/s41586-020-2395-5](https://doi.org/10.1038/s41586-020-2395-5).
90. Stensmyr MC, Dweck HKM, Farhan A, Ibba I, Strutz A, Mukunda L, Linz J, Grabe V, Steck K, Lavista-Llanos S, et al. A conserved dedicated olfactory circuit for detecting harmful microbes in *Drosophila*. *Cell*. 2012;151(6):1345–1357. doi: [10.1016/j.cell.2012.09.046](https://doi.org/10.1016/j.cell.2012.09.046).
91. Ballestriero F, Nappi J, Zampi G, Bazzicalupo P, Di Schiavi E, Egan S. *Caenorhabditis elegans* employs innate and learned aversion in response to bacterial toxic metabolites tambjamine and violacein. *Sci Rep*. 2016;6(1):29284. doi: [10.1038/srep29284](https://doi.org/10.1038/srep29284).
92. Prakash D, Radhika B, Venkatesan R, Chalasani SH, Singh V. 1-undecene from *Pseudomonas aeruginosa* is an olfactory signal for flight-or-flight response in *Caenorhabditis elegans*. *EMBO J*. 2021;40(13):e106938. doi: [10.15252/embj.2020106938](https://doi.org/10.15252/embj.2020106938).
93. Becher PG, Flick G, Rozpędowska E, Schmidt A, Hagman A, Lebreton S, Larsson MC, Hansson BS, Piškur J, Witzgall P, et al. Yeast, not fruit volatiles mediate *Drosophila melanogaster* attraction, oviposition and development. *Funct Ecol*. 2012;26(4):822–828. doi: [10.1111/j.1365-2435.2012.02006.x](https://doi.org/10.1111/j.1365-2435.2012.02006.x).
94. Biasazin TD, Herrera SL, Kimbokota F, Dekker T. Diverging olfactory sensitivities to yeast volatiles reflect resource partitioning of tephritids and drosophilids. *Front Ecol Evol*. 2022;10:999762. doi: [10.3389/fevo.2022.999762](https://doi.org/10.3389/fevo.2022.999762).
95. He M, Chen H, Yang X, Gao Y, Lu Y, Cheng D. Gut bacteria induce oviposition preference through ovipositor recognition in fruit fly. *Commun Biol*. 2022;5(1):973. doi: [10.1038/s42003-022-03947-z](https://doi.org/10.1038/s42003-022-03947-z).
96. Xu L, Lou Q, Cheng C, Lu M, Sun J. Gut-associated bacteria of *Dendroctonus valens* and their involvement in verbenone production. *Microb Ecol*. 2015;70(4):1012–1023. doi: [10.1007/s00248-015-0625-4](https://doi.org/10.1007/s00248-015-0625-4).
97. Xu L, Lu M, Xu D, Chen L, Sun J. Sexual variation of bacterial microbiota of *Dendroctonus valens* guts and frass in relation to verbenone production. *J Insect Physiol*. 2016;95:110–117. doi: [10.1016/j.jinsphys.2016.09.014](https://doi.org/10.1016/j.jinsphys.2016.09.014).
98. Schaeffer RN, Rering CC, Maalouf I, Beck JJ, Vannette RL. Microbial metabolites elicit distinct olfactory and gustatory preferences in bumblebees. *Biol Lett*. 2019;15(7):20190132. doi: [10.1098/rsbl.2019.0132](https://doi.org/10.1098/rsbl.2019.0132).
99. Depetris-Chauvin A, Galagovsky D, Chevalier C, Maniere G, Grosjean Y. Olfactory detection of a bacterial short-chain fatty acid acts as an orexigenic signal in *drosophila melanogaster* larvae. *Sci Rep*. 2017;7(1):14230. doi: [10.1038/s41598-017-14589-1](https://doi.org/10.1038/s41598-017-14589-1).
100. Foster RG, Roenneberg T. Human responses to the geophysical daily, annual and lunar cycles. *Curr Biol*. 2008;18(17):R784–R794. doi: [10.1016/j.cub.2008.07.003](https://doi.org/10.1016/j.cub.2008.07.003).
101. Litichevskiy L, Thaïss CA. The oscillating gut microbiome and its effects on host circadian biology. *Annu Rev Nutr*. 2022;42(1):145–164. doi: [10.1146/annurev-nutr-062320-111321](https://doi.org/10.1146/annurev-nutr-062320-111321).
102. Leone V, Gibbons SM, Martinez K, Hutchison A, Huang E, Cham C, Pierre J, Heneghan A, Nadimpalli A, Hubert N, et al. Effects of diurnal variation of gut microbes and high-fat feeding on host circadian clock function and metabolism. *Cell Host & Microbe*. 2015;17(5):681–689. doi: [10.1016/j.chom.2015.03.006](https://doi.org/10.1016/j.chom.2015.03.006).
103. Murakami M, Tognini P. The circadian clock as an essential molecular link between host physiology and microorganisms. *Front Cell Infect Microbiol*. 2020;9:469. doi: [10.3389/fcimb.2019.00469](https://doi.org/10.3389/fcimb.2019.00469).
104. Frazier K, Chang EB. Intersection of the gut microbiome and circadian rhythms in metabolism. *Trends Endocrinol & Metab*. 2020;31(1):25–36. doi: [10.1016/j.tem.2019.08.013](https://doi.org/10.1016/j.tem.2019.08.013).



105. Thaiss CA, Levy M, Korem T, Dohnalová L, Shapiro H, Jaitin DA, David E, Winter DR, Gury-BenAri M, Tatirovsky E, et al. Microbiota diurnal rhythmicity programs host transcriptome oscillations. *Cell*. 2016;167(6):1495–1510.e12. doi: [10.1016/j.cell.2016.11.003](https://doi.org/10.1016/j.cell.2016.11.003).
106. Lotti S, Dinu M, Colombini B, Amedei A, Sofi F. Circadian rhythms, gut microbiota, and diet: possible implications for health. *Nutr Metab Cardiovasc Dis*. 2023;33(8):1490–1500. doi: [10.1016/j.numecd.2023.05.009](https://doi.org/10.1016/j.numecd.2023.05.009).
107. Montaruli A, Castelli L, Mulè A, Scurati R, Esposito F, Galasso L, Roveda E. Biological rhythm and chronotype: new perspectives in health. *Biomolecules*. 2021;11(4):487. doi: [10.3390/biom11040487](https://doi.org/10.3390/biom11040487).
108. Thaiss CA, Zeevi D, Levy M, Zilberman-Schapira G, Suez J, Tengeler A, Abramson L, Katz M, Korem T, Zmora N, et al. Transkingdom control of microbiota diurnal oscillations promotes metabolic homeostasis. *Cell*. 2014;159(3):514–529. doi: [10.1016/j.cell.2014.09.048](https://doi.org/10.1016/j.cell.2014.09.048).
109. Liang X, Bushman FD, FitzGerald GA. Rhythmicity of the intestinal microbiota is regulated by gender and the host circadian clock. *Proc Natl Acad Sci*. 2015;112(33):10479–10484. doi: [10.1073/pnas.1501305112](https://doi.org/10.1073/pnas.1501305112).
110. Tahara Y, Yamazaki M, Sukigara H, Motohashi H, Sasaki H, Miyakawa H, Haraguchi A, Ikeda Y, Fukuda S, Shibata S. Gut microbiota-derived short chain fatty acids induce circadian clock entrainment in mouse peripheral tissue. *Sci Rep*. 2018;8(1):1395. doi: [10.1038/s41598-018-19836-7](https://doi.org/10.1038/s41598-018-19836-7).
111. Fawad JA, Luzader DH, Hanson GF, Moutinho TJ, McKinney CA, Mitchell PG, Brown-Steinke K, Kumar A, Park M, Lee S, et al. Histone deacetylase inhibition by gut microbe-generated short-chain fatty acids entrains intestinal epithelial circadian rhythms. *Gastroenterology*. 2022;163(5):1377–1390.e11. doi: [10.1053/j.gastro.2022.07.051](https://doi.org/10.1053/j.gastro.2022.07.051).
112. Kaczmarek JL, Musaad SMA, Holscher HD. Time of day and eating behaviors are associated with the composition and function of the human gastrointestinal microbiota. *Am J Clin Nutr*. 2017;106(5):1220–1231. doi: [10.3945/ajcn.117.156380](https://doi.org/10.3945/ajcn.117.156380).
113. Firoozi D, Masoumi SJ, Mohammad-Kazem Hosseini Asl S, Labbe A, Razeghian-Jahromi I, Fararouei M, Lankarani KB, Dara M. Effects of short-chain fatty acid-butyrate supplementation on expression of circadian-clock genes, sleep quality, and inflammation in patients with active ulcerative colitis: a double-blind randomized controlled trial. *Lipids Health Dis*. 2024;23(1):216. doi: [10.1186/s12944-024-02203-z](https://doi.org/10.1186/s12944-024-02203-z).
114. Zwihaft Z, Aviram R, Shalev M, Rouso-Noori L, Kraut-Cohen J, Golik M, Brandis A, Reinke H, Aharoni A, Kahana C, et al. Circadian clock control by polyamine levels through a mechanism that declines with age. *Cell Metab*. 2015;22(5):874–885. doi: [10.1016/j.cmet.2015.09.011](https://doi.org/10.1016/j.cmet.2015.09.011).
115. Zimmermann P, Kurth S, Pugin B, Bokulich NA. Microbial melatonin metabolism in the human intestine as a therapeutic target for dysbiosis and rhythm disorders. *NPJ Biofilms And Microbiomes*. 2024;10(1):139. doi: [10.1038/s41522-024-00605-6](https://doi.org/10.1038/s41522-024-00605-6).
116. Zitting KM, Vetrivelan R, Yuan RK, Vujovic N, Wang W, Bandaru SS, Quan SF, Klerman EB, Scheer FAJL, Buxton OM, et al. Chronic circadian disruption on a high-fat diet impairs glucose tolerance. *Metabolism*. 2022;130:155158. doi: [10.1016/j.metabol.2022.155158](https://doi.org/10.1016/j.metabol.2022.155158).
117. Kohsaka A, Laposky AD, Ramsey KM, Estrada C, Joshu C, Kobayashi Y, Turek FW, Bass J. High-fat diet disrupts behavioral and molecular circadian rhythms in mice. *Cell Metab*. 2007;6(5):414–421. doi: [10.1016/j.cmet.2007.09.006](https://doi.org/10.1016/j.cmet.2007.09.006).
118. Choi H, Rao MC, Chang EB. Gut microbiota as a transducer of dietary cues to regulate host circadian rhythms and metabolism. *Nat Rev Gastroenterol Hepatol*. 2021;18(10):679–689. doi: [10.1038/s41575-021-00452-2](https://doi.org/10.1038/s41575-021-00452-2).
119. Yao L, Seaton SC, Ndousse-Fetter S, Adhikari AA, DiBenedetto N, Mina AI, Banks AS, Bry L, Devlin AS. A selective gut bacterial bile salt hydrolase alters host metabolism. *Elife*. 2018;7:e37182. doi: [10.7554/eLife.37182](https://doi.org/10.7554/eLife.37182).
120. Govindarajan K, MacSharry J, Casey PG, Shanahan F, Joyce SA, Gahan CGM, Makishima M. Unconjugated bile acids influence expression of circadian genes: a potential mechanism for microbe-host crosstalk. *PLOS ONE*. 2016;11(12):e0167319. doi: [10.1371/journal.pone.0167319](https://doi.org/10.1371/journal.pone.0167319).
121. Lahiri S, Kim H, Garcia-Perez I, Reza MM, Martin KA, Kundu P, Cox LM, Selkirk J, Posma JM, Zhang H, et al. The gut microbiota influences skeletal muscle mass and function in mice. *Sci Transl Med*. 2019;11(502):eaan5662. doi: [10.1126/scitranslmed.aan5662](https://doi.org/10.1126/scitranslmed.aan5662).
122. Schretter CE, Vielmetter J, Bartos I, Marka Z, Marka S, Argade S, Mazmanian SK. A gut microbial factor modulates locomotor behaviour in *Drosophila*. *Nature*. 2018;563(7731):402–406. doi: [10.1038/s41586-018-0634-9](https://doi.org/10.1038/s41586-018-0634-9).
123. Weitekamp CA, Kvasnicka A, Keely SP, Brinkman NE, Howey XM, Gaballah S, Phelps D, Catron T, Zurlinden T, Wheaton E, et al. Monoassociation with bacterial isolates reveals the role of colonization, community complexity and abundance on locomotor behavior in larval zebrafish. *Anim Microbiome*. 2021;3(1):1–13. doi: [10.1186/s42523-020-00069-x](https://doi.org/10.1186/s42523-020-00069-x).
124. Zhu F, Guo R, Wang W, Ju Y, Wang Q, Ma Q, Sun Q, Fan Y, Xie Y, Yang Z, et al. Transplantation of microbiota from drug-free patients with schizophrenia causes schizophrenia-like abnormal behaviors and dysregulated kynurenine metabolism in mice. *Mol Psychiatry*. 2020;25(11):2905–2918. doi: [10.1038/s41380-019-0475-4](https://doi.org/10.1038/s41380-019-0475-4).



125. Lai TT, Tsai YH, Liou CW, Fan C-H, Hou Y-T, Yao T-H, Chuang H-L, Wu W-L. The gut microbiota modulate locomotion via vagus-dependent glucagon-like peptide-1 signaling. *NPJ Biofilms Microbiomes*. 2024;10(1):2. doi: [10.1038/s41522-024-00477-w](https://doi.org/10.1038/s41522-024-00477-w).
126. Fortier MÈ, Joobar R, Luheshi GN, Boksa P. Maternal exposure to bacterial endotoxin during pregnancy enhances amphetamine-induced locomotion and startle responses in adult rat offspring. *J Psychiatric Res*. 2004;38(3):335–345. doi: [10.1016/j.jpsychires.2003.10.001](https://doi.org/10.1016/j.jpsychires.2003.10.001).
127. Liu WH, Chuang HL, Huang YT, Wu C-C, Chou G-T, Wang S, Tsai Y-C. Alteration of behavior and monoamine levels attributable to *Lactobacillus plantarum* PS128 in germ-free mice. *Behavioural Brain Res*. 2016;298:202–209. doi: [10.1016/j.bbr.2015.10.046](https://doi.org/10.1016/j.bbr.2015.10.046).
128. Zhang J, Zhao Y, Sun Z, Sun T. *Lactocaseibacillus rhamnosus* Probio-M9 extends the lifespan of *Caenorhabditis elegans*. *Commun Biol*. 2022;5(1):1139. doi: [10.1038/s42003-022-04031-2](https://doi.org/10.1038/s42003-022-04031-2).
129. MacFabe DF, Rodríguez-Capote K, Hoffman JE, Franklin AE, Mohammad-A Y, Taylor AR, Boon F, Cain DP, Kavaliers M, Possmayer F, et al. A novel rodent model of autism: intraventricular infusions of propionic acid increase locomotor activity and induce neuroinflammation and oxidative stress in discrete regions of adult rat brain. *Am J Biochem Biotechnol*. 2008;4(2):146–166. doi: [10.3844/ajbbasp.2008.146.166](https://doi.org/10.3844/ajbbasp.2008.146.166).
130. Ossenkopp KP, Foley KA, Gibson J, Fudge MA, Kavaliers M, Cain DP, MacFabe DF. Systemic treatment with the enteric bacterial fermentation product, propionic acid, produces both conditioned taste avoidance and conditioned place avoidance in rats. *Behavioural Brain Res*. 2012;227(1):134–141. doi: [10.1016/j.bbr.2011.10.045](https://doi.org/10.1016/j.bbr.2011.10.045).
131. Jaglin M, Rhimi M, Philippe C, Pons N, Bruneau A, Goustard B, Dauge V, Maguin E, Naudon L, Rabot S. Indole, a signaling molecule produced by the gut microbiota, negatively impacts emotional behaviors in rats. *Front Neurosci*. 2018;12:216. doi: [10.3389/fnins.2018.00216](https://doi.org/10.3389/fnins.2018.00216).
132. Guth L, Zhang Z, DiProspero NA, Joubin K, Fitch MT. Spinal cord injury in the rat: treatment with bacterial lipopolysaccharide and indomethacin enhances cellular repair and locomotor function. *Exp Neurol*. 1994;126(1):76–87. doi: [10.1006/exnr.1994.1043](https://doi.org/10.1006/exnr.1994.1043).
133. Marullo AL, O'Halloran KD. Microbes, metabolites and muscle: Is the gut–muscle axis a plausible therapeutic target in Duchenne muscular dystrophy? *Exp Physiol*. 2023;108(9):1132–1143. doi: [10.1113/EP091063](https://doi.org/10.1113/EP091063).
134. Comizzoli P, Power M. Reproductive microbiomes in wild animal species: a new dimension in conservation biology. *Reprod Sci Ani Con*. 2019;1200:225–240. doi: [10.1007/978-3-030-23633-5\\_8](https://doi.org/10.1007/978-3-030-23633-5_8).
135. Comizzoli P, Power ML, Bornbusch SL, Muletz-Wolz CR. Interactions between reproductive biology and microbiomes in wild animal species. *Anim Microbiome*. 2021;3(1):87. doi: [10.1186/s42523-021-00156-7](https://doi.org/10.1186/s42523-021-00156-7).
136. Reid G, Brigidi P, Burton JP, Contractor N, Duncan S, Fargier E, Hill C, Lebeer S, Martin R, McBain AJ, et al. Microbes central to human reproduction. *Am J Reprod Immunol*. 2015;73(1):1–11. doi: [10.1111/aji.12319](https://doi.org/10.1111/aji.12319).
137. Salia S, Martin Y, Burke FF, Myles LA, Jackman L, Halievski K, Bambico FR, Swift-Gallant A. Antibiotic-induced socio-sexual behavioral deficits are reversed via cecal microbiota transplantation but not androgen treatment. *Brain Behav Immun-Health*. 2023;30:100637. doi: [10.1016/j.bbih.2023.100637](https://doi.org/10.1016/j.bbih.2023.100637).
138. Tirandaz H, Ebrahim-Habibi MB, Moradveisi B, Raoofi S, Salehi-Najafabadi A, Mohammadi E. Microbiota potential for the treatment of sexual dysfunction. *Med Hypotheses*. 2018;115:46–49. doi: [10.1016/j.mehy.2018.03.021](https://doi.org/10.1016/j.mehy.2018.03.021).
139. Rowe M, Veerus L, Trosvik P, Buckling A, Pizzari T. The reproductive microbiome: an emerging driver of sexual selection, sexual conflict, mating systems, and reproductive isolation. *Trends Ecol & Evol*. 2020;35(3):220–234. doi: [10.1016/j.tree.2019.11.004](https://doi.org/10.1016/j.tree.2019.11.004).
140. Delbare SYN, Ahmed-Braimah YH, Wolfner MF, Clark AG. Interactions between the microbiome and mating influence the female's transcriptional profile in *Drosophila melanogaster*. *Sci Rep*. 2020;10(1):18168. doi: [10.1038/s41598-020-75156-9](https://doi.org/10.1038/s41598-020-75156-9).
141. Elgart M, Stern S, Salton O, Gnainsky Y, Heifetz Y, Soen Y. Impact of gut microbiota on the fly's germ line. *Nat Commun*. 2016;7(1):11280. doi: [10.1038/ncomms11280](https://doi.org/10.1038/ncomms11280).
142. Segata N, Baldini F, Pompon J, Garrett WS, Truong DT, Dabiré RK, Diabaté A, Levashina EA, Catteruccia F. The reproductive tracts of two malaria vectors are populated by a core microbiome and by gender- and swarm-enriched microbial biomarkers. *Sci Rep*. 2016;6(1):24207. doi: [10.1038/srep24207](https://doi.org/10.1038/srep24207).
143. Cai H, Cao X, Qin D, Liu Y, Liu Y, Hua J, Peng S. Gut microbiota supports male reproduction via nutrition, immunity, and signaling. *Front Microbiol*. 2022;13:977574. doi: [10.3389/fmicb.2022.977574](https://doi.org/10.3389/fmicb.2022.977574).
144. Qi X, Yun C, Pang Y, Qiao J. The impact of the gut microbiota on the reproductive and metabolic endocrine system. *Gut Microbes*. 2021;13(1):1894070. doi: [10.1080/19490976.2021.1894070](https://doi.org/10.1080/19490976.2021.1894070).
145. Wang S, Fu W, Zhao X, Chang X, Liu H, Zhou L, Li J, Cheng R, Wu X, Li X, et al. Zearalenone disturbs the reproductive-immune axis in pigs: the role of gut microbial metabolites. *Microbiome*. 2022;10(1):234. doi: [10.1186/s40168-022-01397-7](https://doi.org/10.1186/s40168-022-01397-7).
146. Venzon M, Das R, Luciano DJ, Burnett J, Park HS, Devlin JC, Kool ET, Belasco JG, Hubbard EJA, Cadwell K. Microbial byproducts determine reproductive fitness of free-living and parasitic nematodes. *Cell Host & Microbe*. 2022;30(6):786–797.e8. doi: [10.1016/j.chom.2022.03.015](https://doi.org/10.1016/j.chom.2022.03.015).



147. Zhang MY, Zhang XH, Wang XY, Liu Y-L, An J-H, Wang D-H, Cai Z-G, Hou R. Intestinal acetic acid regulates the synthesis of sex pheromones in captive giant pandas. *Front Microbiol.* **2023**;14:14. doi: [10.3389/fmicb.2023.1234676](https://doi.org/10.3389/fmicb.2023.1234676).
148. Chen YC, Seyedsayamdost MR, Ringstad N. A microbial metabolite synergizes with endogenous serotonin to trigger *C. elegans* reproductive behavior. *Proc Natl Acad Sci.* **2020**;117(48):30589–30598. doi: [10.1073/pnas.2017918117](https://doi.org/10.1073/pnas.2017918117).
149. Liu W, Wang J, Zhang H, Yang Y-C, Kang R-X, Bai P, Fu H, Chen L-R, Gao Y-P, Tan EK. Symbiotic bacteria attenuate *Drosophila* oviposition repellence to alkaline through acidification. *Insect Sci.* **2021**;28(2):403–414. doi: [10.1111/1744-7917.12857](https://doi.org/10.1111/1744-7917.12857).
150. Shu R, Hahn DA, Jurkevitch E, Liburd OE, Yuval B, Wong ACN. Sex-dependent effects of the microbiome on foraging and locomotion in *Drosophila suzukii*. *Front Microbiol.* **2021**;12:656406. doi: [10.3389/fmicb.2021.656406](https://doi.org/10.3389/fmicb.2021.656406).
151. Gnainsky Y, Zfanya N, Elgart M, Omri E, Brandis A, Mehlman T, Itkin M, Malitsky S, Adamski J, Soen Y. Systemic regulation of host energy and oogenesis by microbiome-derived mitochondrial coenzymes. *Cell Rep.* **2021**;34(1):108583. doi: [10.1016/j.celrep.2020.108583](https://doi.org/10.1016/j.celrep.2020.108583).
152. Gullledge L, Oyeboode D, Donaldson JR. The influence of the microbiome on aggressive behavior: an insight into age-related aggression. *FEMS Microbiol Lett.* **2023**;370:fnac114. doi: [10.1093/femsle/fnac114](https://doi.org/10.1093/femsle/fnac114).
153. Jia Y, Jin S, Hu K, Geng L, Han C, Kang R, Pang Y, Ling E, Tan EK, Pan Y, et al. Gut microbiome modulates *Drosophila* aggression through octopamine signaling. *Nat Commun.* **2021**;12(1):2698. doi: [10.1038/s41467-021-23041-y](https://doi.org/10.1038/s41467-021-23041-y).
154. Mikami K, Watanabe N, Tochio T, Kimoto K, Akama F, Yamamoto K. Impact of gut microbiota on host aggression: potential applications for therapeutic interventions early in development. *Microorganisms.* **2023**;11(4):1008. doi: [10.3390/microorganisms11041008](https://doi.org/10.3390/microorganisms11041008).
155. Chen S, Yan C, Liu W, Chen K, Xing L, Li H, Zhao X. Research note: integrated gut microbiome and short-chain fatty acids responds to dominance hierarchy in roosters. *Poult Sci.* **2022**;101(3):101670. doi: [10.1016/j.psj.2021.101670](https://doi.org/10.1016/j.psj.2021.101670).
156. Fu Y, Hu J, Erasmus MA, Zhang H, Johnson TA, Cheng H. Cecal microbiota transplantation: unique influence of cecal microbiota from divergently selected inbred donor lines on cecal microbial profile, serotonergic activity, and aggressive behavior of recipient chickens. *J Anim Sci Biotechnol.* **2023**;14(1):66. doi: [10.1186/s40104-023-00866-9](https://doi.org/10.1186/s40104-023-00866-9).
157. Hu J, Johnson TA, Zhang H, Cheng HW. The microbiota–gut–brain axis: gut microbiota modulates conspecific aggression in diversely selected laying hens. *Microorganisms.* **2022**;10(6):1081. doi: [10.3390/microorganisms10061081](https://doi.org/10.3390/microorganisms10061081).
158. Rohrscheib CE, Bondy E, Josh P, Riegler M, Eyles D, van Swinderen B, Weible MW, Brownlie JC. Wolbachia influences the production of octopamine and affects *Drosophila* male aggression. *Appl Environ Microbiol.* **2015**;81(14):4573–4580. doi: [10.1128/AEM.00573-15](https://doi.org/10.1128/AEM.00573-15).
159. Verbeek E, Keeling L, Landberg R, Lindberg JE, Dicksved J. The gut microbiota and microbial metabolites are associated with tail biting in pigs. *Sci Rep.* **2021**;11(1):20547. doi: [10.1038/s41598-021-99741-8](https://doi.org/10.1038/s41598-021-99741-8).
160. Meyer B, Zentek J, Harlander-Matauschek A. Differences in intestinal microbial metabolites in laying hens with high and low levels of repetitive feather-pecking behavior. *Physiol Behav.* **2013**;110:111:96–101. doi: [10.1016/j.physbeh.2012.12.017](https://doi.org/10.1016/j.physbeh.2012.12.017).
161. Choi J, Lee S, Won J, Jin Y, Hong Y, Hur T-Y, Kim J-H, Lee S-R, Hong Y. Pathophysiological and neurobehavioral characteristics of a propionic acid-mediated autism-like rat model. *PLOS ONE.* **2018**;13(2):e0192925. doi: [10.1371/journal.pone.0192925](https://doi.org/10.1371/journal.pone.0192925).
162. Deng H, He L, Wang C, Zhang T, Guo H, Zhang H, Song Y, Chen B. Altered gut microbiota and its metabolites correlate with plasma cytokines in schizophrenia inpatients with aggression. *BMC Psychiatry.* **2022**;22(1):1–12. doi: [10.1186/s12888-022-04255-w](https://doi.org/10.1186/s12888-022-04255-w).
163. Sobko T, Reinders CI, Jansson EÅ, Norin E, Midtvedt T, Lundberg JO. Gastrointestinal bacteria generate nitric oxide from nitrate and nitrite. *Nitric Oxide.* **2005**;13(4):272–278. doi: [10.1016/j.niox.2005.08.002](https://doi.org/10.1016/j.niox.2005.08.002).
164. Tiso M, Schechter AN, Jourde'heuil D. Nitrate reduction to nitrite, nitric oxide and ammonia by gut bacteria under physiological conditions. *PLOS ONE.* **2015**;10(3):e0119712. doi: [10.1371/journal.pone.0119712](https://doi.org/10.1371/journal.pone.0119712).
165. Chiavegatto S, Nelson RJ. Interaction of nitric oxide and serotonin in aggressive behavior. *Horm Behav.* **2003**;44(3):233–241. doi: [10.1016/j.yhbeh.2003.02.002](https://doi.org/10.1016/j.yhbeh.2003.02.002).
166. Needham BD, Tang W, Wu W. Searching for the gut microbial contributing factors to social behavior in rodent models of autism spectrum disorder. *Dev Neurobiol.* **2018**;78(5):474–499. doi: [10.1002/dneu.22581](https://doi.org/10.1002/dneu.22581).
167. Sherwin E, Bordenstein SR, Quinn JL, Dinan TG, Cryan JF. Microbiota and the social brain. *Science.* **2019**;366(6465):eaar 2016. doi: [10.1126/science.aar2016](https://doi.org/10.1126/science.aar2016).
168. Archie EA, Tung J. Social behavior and the microbiome. *Curr Opin Behav Sci.* **2015**;6:28–34. doi: [10.1016/j.cobeha.2015.07.008](https://doi.org/10.1016/j.cobeha.2015.07.008).
169. Theis KR, Venkataraman A, Dycus JA, Koonter KD, Schmitt-Matzen EN, Wagner AP, Holekamp KE, Schmidt TM. Symbiotic bacteria appear to mediate hyena social odors. *Proc Natl Acad Sci.* **2013**;110(49):19832–19837. doi: [10.1073/pnas.1306477110](https://doi.org/10.1073/pnas.1306477110).
170. Rojas CA, Holekamp KE, Winters AD, Theis KR. Body site-specific microbiota reflect sex and age-class among



- wild spotted hyenas. *FEMS Microbiol Ecol.* **2020**;96(2): fiae007. doi: [10.1093/femsec/fiae007](https://doi.org/10.1093/femsec/fiae007).
171. Perofsky AC, Lewis RJ, Abondano LA, Di Fiore A, Meyers LA. Hierarchical social networks shape gut microbial composition in wild Verreaux's sifaka. *Proc R Soc B Biol Sci.* **2017**;284(1868):20172274. doi: [10.1098/rspb.2017.2274](https://doi.org/10.1098/rspb.2017.2274).
  172. Matsuda Y, Ozawa N, Shinozaki T, Wakabayashi K-I, Suzuki K, Kawano Y, Ohtsu I, Tatebayashi Y. Ergothioneine, a metabolite of the gut bacterium *Lactobacillus reuteri*, protects against stress-induced sleep disturbances. *Transl Psychiatry.* **2020**;10(1):170. doi: [10.1038/s41398-020-0855-1](https://doi.org/10.1038/s41398-020-0855-1).
  173. Liou CW, Cheng SJ, Yao TH, Lai T-T, Tsai Y-H, Chien C-W, Kuo Y-L, Chou S-H, Hsu C-C, Wu W-L. Microbial metabolites regulate social novelty via CaMKII neurons in the BNST. *Brain Behav Immun.* **2023**;113:104–123. doi: [10.1016/j.bbi.2023.06.029](https://doi.org/10.1016/j.bbi.2023.06.029).
  174. Luo Y, Zhao P, Dou M, Mao J, Zhang G, Su Y, Wang Q, Wang Q, Wang Y, Sun R, et al. Exogenous microbiota-derived metabolite trimethylamine N-oxide treatment alters social behaviors: involvement of hippocampal metabolic adaptation. *Neuropharmacology.* **2021**;191:108563. doi: [10.1016/j.neuropharm.2021.108563](https://doi.org/10.1016/j.neuropharm.2021.108563).
  175. Laue HE, Bauer JA, Pathmasiri W, Sumner SCJ, McRitchie S, Palys TJ, Hoen AG, Madan JC, Karagas MR. Patterns of infant fecal metabolite concentrations and social behavioral development in toddlers. *Pediatr Res.* **2024**;96(1):1–8. doi: [10.1038/s41390-024-03129-z](https://doi.org/10.1038/s41390-024-03129-z).
  176. Huang L, Duan C, Xia X, Wang H, Wang Y, Zhong Z, Wang B, Ding W, Yang Y. Commensal microbe-derived propionic acid mediates juvenile social isolation-induced social deficits and anxiety-like behaviors. *Brain Res Bull.* **2021**;166:161–171. doi: [10.1016/j.brainresbull.2020.12.001](https://doi.org/10.1016/j.brainresbull.2020.12.001).
  177. Gacias M, Gaspari S, Santos PMG, Tamburini S, Andrade M, Zhang F, Shen N, Tolstikov V, Kiebish MA, Dupree JL, et al. Microbiota-driven transcriptional changes in prefrontal cortex override genetic differences in social behavior. *Elife.* **2016**;5: e13442. doi: [10.7554/eLife.13442](https://doi.org/10.7554/eLife.13442).
  178. Hou J, Hull V, Fujimoto M, Zhang Z, Chen X, Chen S, Chen R, Connor T, Qi D, Zhang J. Characterizing the metabolome and microbiome at giant panda scent marking sites during the mating season. *iScience.* **2024**;27(6):110051. doi: [10.1016/j.isci.2024.110051](https://doi.org/10.1016/j.isci.2024.110051).
  179. Hagey L, MacDonald E. Chemical cues identify gender and individuality in giant pandas (*Ailuropoda melanoleuca*). *J Chem Ecol.* **2003**;29(6):1479–1488. doi: [10.1023/A:1024225806263](https://doi.org/10.1023/A:1024225806263).
  180. Yuan H, Liu D, Sun L, Wei R, Zhang G, Sun R. Anogenital gland secretions code for sex and age in the giant panda, *Ailuropoda melanoleuca*. *Can J Zool.* **2004**;82(10):1596–1604. doi: [10.1139/z04-144](https://doi.org/10.1139/z04-144).
  181. Engl T, Kaltenpoth M. Influence of microbial symbionts on insect pheromones. *Nat Prod Rep.* **2018**;35(5):386–397. doi: [10.1039/C7NP00068E](https://doi.org/10.1039/C7NP00068E).
  182. Tesse S, van Zweden JS, Pontieri L, Kooij PW, Sørensen SJ, Wenseleers T, Poulsen M, Boomsma JJ, Sapountzis P. The scent of symbiosis: gut bacteria may affect social interactions in leaf-cutting ants. *Anim Behaviour.* **2019**;150:239–254. doi: [10.1016/j.anbehav.2018.12.017](https://doi.org/10.1016/j.anbehav.2018.12.017).
  183. Matsuura K. Nestmate recognition mediated by intestinal bacteria in a termite, *reticulitermes speratus*. *Oikos.* **2001**;92(1):20–26. doi: [10.1034/j.1600-0706.2001.920103.x](https://doi.org/10.1034/j.1600-0706.2001.920103.x).
  184. Zheng X, Cai X, Hao H. Emerging targetome and signalome landscape of gut microbial metabolites. *Cell Metab.* **2022**;34(1):35–58. doi: [10.1016/j.cmet.2021.12.011](https://doi.org/10.1016/j.cmet.2021.12.011).
  185. Tan JK, McKenzie C, Mariño E, Macia L, Mackay CR. Metabolite-sensing G protein-coupled receptors—facilitators of diet-related immune regulation. *Annu Rev Immunol.* **2017**;35(1):371–402. doi: [10.1146/annurev-immunol-051116-052235](https://doi.org/10.1146/annurev-immunol-051116-052235).
  186. Aleti G, Troyer EA, Hong S. G protein-coupled receptors: a target for microbial metabolites and a mechanistic link to microbiome-immune-brain interactions. *Brain Behav Immun-Health.* Published online 2023:100671. **2023**;32:100671. doi: [10.1016/j.bbih.2023.100671](https://doi.org/10.1016/j.bbih.2023.100671).
  187. Scott SA, Fu J, Chang PV. Microbial tryptophan metabolites regulate gut barrier function via the aryl hydrocarbon receptor. *Proc Natl Acad Sci.* **2020**;117(32):19376–19387. doi: [10.1073/pnas.2000047117](https://doi.org/10.1073/pnas.2000047117).
  188. Ma N, He T, Johnston LJ, Ma X. Host-microbiome interactions: the aryl hydrocarbon receptor as a critical node in tryptophan metabolites to brain signaling. *Gut Microbes.* **2020**;11(5):1203–1219. doi: [10.1080/19490976.2020.1758008](https://doi.org/10.1080/19490976.2020.1758008).
  189. Venkatesh M, Mukherjee S, Wang H, Li H, Sun K, Benechet A, Qiu Z, Maher L, Redinbo M, Phillips R, et al. Symbiotic bacterial metabolites regulate gastrointestinal barrier function via the xenobiotic sensor PXR and Toll-like receptor 4. *Immunity.* **2014**;41(2):296–310. doi: [10.1016/j.immuni.2014.06.014](https://doi.org/10.1016/j.immuni.2014.06.014).
  190. Xiao HW, Cui M, Li Y, Dong J-L, Zhang S-Q, Zhu C-C, Jiang M, Zhu T, Wang B, Wang H-C, et al. Gut microbiota-derived indole 3-propionic acid protects against radiation toxicity via retaining acyl-CoA-binding protein. *Microbiome.* **2020**;8(1):1–17. doi: [10.1186/s40168-020-00845-6](https://doi.org/10.1186/s40168-020-00845-6).
  191. Zheng L, Kelly CJ, Battista KD, Schaefer R, Lanis JM, Alexeev EE, Wang RX, Onyiah JC, Kominsky DJ, Colgan SP. Microbial-derived butyrate promotes epithelial barrier function through IL-10 receptor-dependent repression of claudin-2. *J Immunol.* **2017**;199(8):2976–2984. doi: [10.4049/jimmunol.1700105](https://doi.org/10.4049/jimmunol.1700105).



192. Shelton CD, Sing E, Mo J, Shealy NG, Yoo W, Thomas J, Fitz GN, Castro PR, Hickman TT, Torres TP, et al. An early-life microbiota metabolite protects against obesity by regulating intestinal lipid metabolism. *Cell Host & Microbe*. 2023;31(10):1604–1619.e10. doi: [10.1016/j.chom.2023.09.002](https://doi.org/10.1016/j.chom.2023.09.002).
193. Ng R, Kalinousky A, Harris J. Epigenetics of cognition and behavior: insights from Mendelian disorders of epigenetic machinery. *J Neurodev Disord*. 2023;15(1):16. doi: [10.1186/s11689-023-09482-0](https://doi.org/10.1186/s11689-023-09482-0).
194. Elvir L, Duclot F, Wang Z, Kabbaj M. Epigenetic regulation of motivated behaviors by histone deacetylase inhibitors. *Neurosci Biobehav Rev*. 2019;105:305–317. doi: [10.1016/j.neubiorev.2017.09.030](https://doi.org/10.1016/j.neubiorev.2017.09.030).
195. Kundu P, Torres ERS, Stagaman K, Kasschau K, Okhovat M, Holden S, Ward S, Nevonen KA, Davis BA, Saito T, et al. Integrated analysis of behavioral, epigenetic, and gut microbiome analyses in App NL-GF, App NL-F, and wild type mice. *Sci Rep*. 2021;11(1):4678. doi: [10.1038/s41598-021-83851-4](https://doi.org/10.1038/s41598-021-83851-4).
196. Yang J, Tang R, Chen S, Chen Y, Yuan K, Huang R, Wang L. Exposure to high-sugar diet induces trans-generational changes in sweet sensitivity and feeding behavior via H3K27me3 reprogramming. *Elife*. 2023;12:e85365. doi: [10.7554/eLife.85365](https://doi.org/10.7554/eLife.85365).
197. Pereira AG, Gracida X, Kagias K, Zhang YC. *C. elegans* aversive olfactory learning generates diverse intergenerational effects. *J Neurogenet*. 2020;34(3–4):378–388. doi: [10.1080/01677063.2020.1819265](https://doi.org/10.1080/01677063.2020.1819265).
198. Krautkramer KA, Dhillon RS, Denu JM, Carey HV. Metabolic programming of the epigenome: host and gut microbial metabolite interactions with host chromatin. *Transl Res*. 2017;189:30–50. doi: [10.1016/j.trsl.2017.08.005](https://doi.org/10.1016/j.trsl.2017.08.005).
199. Krautkramer KA, Kreznar JH, Romano KA, Vivas EI, Barrett-Wilt GA, Rabaglia ME, Keller MP, Attie AD, Rey FE, Denu JM. Diet-microbiota interactions mediate global epigenetic programming in multiple host tissues. *Mol Cell*. 2016;64(5):982–992. doi: [10.1016/j.molcel.2016.10.025](https://doi.org/10.1016/j.molcel.2016.10.025).
200. Gerhauser C. Impact of dietary gut microbial metabolites on the epigenome. *Phil Trans R Soc B Biol Sci*. 2018;373(1748):20170359. doi: [10.1098/rstb.2017.0359](https://doi.org/10.1098/rstb.2017.0359).
201. Hullar MAJ, Fu BC. Diet, the gut microbiome, and epigenetics. *Cancer J*. 2014;20(3):170. doi: [10.1097/PPO.0000000000000053](https://doi.org/10.1097/PPO.0000000000000053).
202. Kumar H, Lund R, Laiho A, Lundelin K, Ley RE, Isolauri E, Salminen S. Gut microbiota as an epigenetic regulator: pilot study based on whole-genome methylation analysis. *mBio*. 2014;5(6):10–1128. doi: [10.1128/mBio.02113-14](https://doi.org/10.1128/mBio.02113-14).
203. Stilling RM, Dinan TG, Cryan JF. Microbial genes, brain & behaviour – epigenetic regulation of the gut-brain axis. *Genes Brain Behav*. 2014;13(1):69–86. doi: [10.1111/gbb.12109](https://doi.org/10.1111/gbb.12109).
204. Romano KA, Martinez-Del Campo A, Kasahara K, Chittim CL, Vivas EI, Amador-Nogues D, Balskus EP, Rey FE. Metabolic, epigenetic, and transgenerational effects of gut bacterial choline consumption. *Cell Host & Microbe*. 2017;22(3):279–290.e7. doi: [10.1016/j.chom.2017.07.021](https://doi.org/10.1016/j.chom.2017.07.021).