The gut microbiota has the capacity to affect host appetite via intestinal satiety pathways, as well as complex feeding behaviors. In this Review, we highlight recent evidence that the gut microbiota can modulate food preference across model organisms. We discuss effects of the gut microbiota on the vagus nerve and brain regions including the hypothalamus, mesolimbic system, and prefrontal cortex, which play key roles in regulating feeding behavior. Crosstalk between commensal bacteria and the central and peripheral nervous systems is associated with alterations in signaling of neurotransmitters and neuropeptides such as dopamine, brain-derived neurotrophic factor (BDNF), and glucagon-like peptide-1 (GLP-1). We further consider areas for future research on mechanisms by which gut microbes may influence feeding behavior involving these neural pathways. Understanding roles for the gut microbiota in feeding regulation will be important for informing therapeutic strategies to treat metabolic and eating disorders.
Roles for the gut microbiota in regulating neuronal feeding circuits

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The gut microbiota has the capacity to affect host appetite via intestinal satiety pathways, as well as complex feeding behaviors. In this Review, we highlight recent evidence that the gut microbiota can modulate food preference across model organisms. We discuss effects of the gut microbiota on the vagus nerve and brain regions including the hypothalamus, mesolimbic system, and prefrontal cortex, which play key roles in regulating feeding behavior. Crosstalk between commensal bacteria and the central and peripheral nervous systems is associated with alterations in signaling of neurotransmitters and neuropeptides such as dopamine, brain-derived neurotrophic factor (BDNF), and glucagon-like peptide-1 (GLP-1). We further consider areas for future research on mechanisms by which gut microbes may influence feeding behavior involving these neural pathways. Understanding roles for the gut microbiota in feeding regulation will be important for informing therapeutic strategies to treat metabolic and eating disorders.

Introduction
Understanding the biological bases of feeding behaviors is key to developing treatments for increasingly prevalent metabolic and eating disorders, including obesity and anorexia nervosa (1–3). Neurobiological regulation of feeding behavior is extremely complex, involving both energy homeostasis and motivational processes (1–6). Neural pathways that regulate feeding behavior have accordingly been divided into homeostatic and non-homeostatic controls (1, 6). Homeostatic controls respond to energy and other metabolic deficits, and classically involve the hypothalamus and brainstem nuclei (1, 2). Non-homeostatic controls involve hedonic and cognitive aspects of feeding that are processed by higher-order brain structures including frontal cortical regions, mesolimbic circuitry, and hippocampus (1, 6). Blurring this artificial division, neural substrates in either category may interact, and both respond to energy status cues and modulate learned feeding behaviors (1). The vagus nerve, which conducts information bidirectionally between the brain and viscera including the gastrointestinal tract, also connects homeostatic and non-homeostatic feeding regulation by communicating gastrointestinal hunger and satiety signals while modulating higher-order brain regions (7–10).

Adding to this already complex system, ingested nutrients also fuel the trillions of microorganisms that inhabit the host gastrointestinal tract, collectively known as the gut microbiota (11, 12). It logically follows that gut microbes may influence host feeding behavior to promote their own fitness (11, 12). Foundational studies in which germ-free mice showed increased body fat after colonization with microbiotas from obese mice or humans compared with their lean counterparts demonstrated a key role for the gut microbiota in the development of obesity (13, 14). Since then, the gut microbiota has been increasingly appreciated as regulating host metabolism (15–19) and appetite (11, 20), with translational implications for both obesity (6, 21–23) and eating disorders (24–27). Microbiota-derived metabolites and bacterial components can influence host appetite via intestinal satiety pathways (11, 20). Despite their known effects on host brain and behavior through the microbiota-gut-brain axis (28–30), the mechanisms by which gut microbes influence feeding behavior, such as nutrient preference or food cravings, remain unclear (12, 13).

This article reviews recent literature reporting effects of the gut microbiota on brain regions involved in homeostatic and non-homeostatic controls (Figure 1 and Tables 1 and 2) and on the vagus nerve (Figure 2). It further explores areas for future research on potential mechanisms by which gut microbes may influence host feeding behavior.

Gut microbial effects on food preference
The gut microbiota can influence host dietary preference across animal models (12, 20). Recent invertebrate studies demonstrated that microbially derived metabolites modulate host feeding behavior, providing potential insight into similar pathways in higher organisms. Colonization of Caenorhabditis elegans with the commensal bacterium Providencia alters host olfactory behavior in response to a volatile repellent called octanol through the production of tyramine (31). Host enzymes convert bacterially produced tyramine to octopamine, which acts on receptors on octanol-sensing nociceptive neurons, resulting in decreased host aversion to octanol and preference for Providencia in food choice assays (31). Similarly to tyramine, bacterially produced lactate can alter host feeding decisions in Drosophila melanogaster (32). Colonization of flies with the commensal bacteria Acetobacter pomorum and Lactobacillus plantarum suppresses yeast appetite of the host when it is deprived of essential amino acids (32, 33). A. pomorum uses lactate produced by L. plantarum to synthesize unidentified metabolites...
that are required to alter host food choice (32). Together, these studies suggest that molecules produced from both host-bacterial and bacterial-bacterial metabolic interactions can modify host sensory and feeding behavior.

In mammals such as mice, a few correlational studies suggest that the microbiota can affect host taste and thus food choice (12, 20, 34). Compared with mice with a conventional microbiota (conventionally raised [CONV-R]), mice raised in the absence of the gut microbiota (germ free [GF]) show increased sucrose intake and upregulation of intestinal sweet taste receptors and glucose transporter (35). The type 2 family of taste receptors (T2Rs), which mediate bitter taste, are activated by bacterial signaling molecules in the respiratory tract (34). Since T2Rs are also expressed in the intestine and regulate GI functions, bacterial interactions with these receptors have been hypothesized but remain to be proven. Although these taste receptors are extraoral (34, 35), they impact food intake (36) and open the possibility for microbial influence on oral taste. A recent study showed that prebiotic treatment with inulin-type fructans can affect host sweet taste perception in mice (37). Prebiotic treatment partially corrects blunted sweet taste perception in diet-induced obese mice by increasing sucrose preference and also ameliorates gut microbiota dysbiosis, suggesting a correlation between taste and gut microbiota composition (37). In addition to taste, endocannabinoid signaling (38–40) may be another possible avenue for gut microbes to affect host food preference (41). Future studies are needed to evaluate causal effects of the gut microbiota on host taste and food preference in mammals.

These include assessing whether microbial molecules can interact with oral and intestinal taste receptors and identifying specific bacteria that can modulate food preference in GF mice.

Gut microbiota and homeostatic feeding controls

Hypothalamus. The hypothalamus is critical for maintaining energy homeostasis by integrating environmental, sensory, hormonal, and gastrointestinal nutrient signals to regulate feeding behavior (1, 6, 8). In particular, two cell populations of the arcuate nucleus (ARC) work antagonistically to control feeding: the anorexigenic (appetite-reducing) pro-opiomelanocortin-expressing (POMC-expressing) neurons and the orexigenic (appetite-stimulating) agouti-related protein/neuropeptide Y-coexpressing (AgRP/NPY-coexpressing) neurons (1, 42). Beyond these neurons, the hypothalamus exhibits functional connectivity to many brain regions to enable coordinated cellular responses to internal metabolic states (43–45).

The gut microbiota’s key role in host metabolism (15–19) has raised the question of whether it may modify hypothalamic activity. Increases in the taxonomic diversity of the gut microbiota significantly correlate with sparing of hypothalamic brain microstructure in obese and nonobese individuals (46), suggesting that the gut microbiota may modulate hypothalamic function in humans. Supporting this notion, several animal studies have demonstrated the capacity of the gut microbiota to alter hypothalamic gene expression, neuropeptide and neurotransmitter levels, and neuronal activity. GF mice exhibit altered hypothalamic expression of feeding-related neuropeptides compared with CONV-R mice (47, 48). In one study, CONV-R mice showed decreased expression of the anorexigenic neuropeptide brain-derived neurotrophic factor (BDNF) in the hypothalamus compared with GF mice, which potentially contributes to fat mass induction by the gut microbiota (47). Secondary to elevated fat mass, CONV-R mice show a compensatory decrease in the expression of orexigenic Npy and Agrp, increase in anorexigenic Pomc and Cart, and increase in leptin resistance–associated Socs-3 compared with GF mice (47). In contrast, another study found that GF mice show higher hypothalamic Pomc and Socs-3 expression than CONV-R mice (48). This discrepancy can potentially be explained by differences in diet composition and other rearing conditions (47, 48). Proteomic analysis of the hypothalamus revealed differences in neuropeptide levels between CONV-R and GF mice, and differential abundance of proteins related to the regulation of transmitter release, signaling pathways, and synapses (49). In addition, GF mice conventionalized with microorganisms from CONV-R mice exhibit upregulation of hypothalamic genes related to extracellular matrix (ECM) function compared with GF mice, suggesting that ECM modification may contribute to gut microbial effects on the hypothalamus (50).

While the precise mechanisms by which the gut microbiota alters hypothalamic physiology are poorly understood, direct actions of microbial metabolism and associated microbiota-
derived molecules may be involved. In piglets, increased carbohydrate availability decreases gut microbial metabolism of aromatic amino acids (AAAs), which makes systemic AAAs more available for synthesis of neurotransmitters such as serotonin (5-HT), dopamine, and BDNF in the hypothalamus (51, 52). Microbial fermentation of nondigestible carbohydrates produces the short-chain fatty acids (SCFAs) acetate, propionate, and butyrate (53). SCFA administration reduces energy intake in rodent and human studies (54), potentially via direct effects on central neurons (acetate) or indirect signaling through peripheral circuits (propionate, butyrate) that innervate the hypothalamus (54–57). One key caveat regarding these studies is that SCFA administration leads to supraphysiological concentrations in the periphery, as the majority of endogenously produced SCFAs are metabolized by the colon and liver (53, 54). Intraportal injection of acetate in mice reduces food intake and alters hypothalamic neuronal activity, gene expression, and neurotransmission (55). Dietary propionate supplementation induces the neuronal immediate-early activation marker c-Fos in hypothalamic nuclei, including the ARC and parabrachial nucleus, but, interestingly, does not appear to alter food intake in rats (56). Oral butyrate administration in mice reduces food intake, which requires intact vagal nerve signaling, and decreases c-Fos expression in hypothalamic NPY neurons (57). In addition to their neuronal effects, SCFAs also modulate glucose homeostasis (53, 56), and brain glucose sensing plays an important role in both homeostatic and hedonic feeding control (58, 59). Similarly to SCFAs, E. coli stationary-phase proteins acutely suppress food intake and induce c-Fos in hypothalamic POMC neurons in the ARC in rats (60). In particular, ClpB (bacterial mimetic of α-MSH, a cleaved product of POMC) stimulates the firing rate of hypothalamic POMC neurons (60). In summary, the gut microbiota regulates hypothalamic functions, and SCFAs and ClpB are promising candidate molecules that alter host feeding behavior via hypothalamic neurons. Further investigations into the neural pathways by which these molecules cause appetite suppression are warranted.

**Brainstem.** The brainstem processes energy-balance signals from the vagus nerve, circulating hormones, and metabolites, as well as descending signals from the midbrain and forebrain, and further relays the information to control motor, autonomic, and endocrine functions involved in feeding (1, 8, 61). A key feeding-related brainstem nucleus is the nucleus of the solitary tract (NTS), which receives inputs from vagal gastrointestinal afferents and produces outputs to both homeostatic brain regions such as the ARC and dorsal motor nucleus of the vagus and higher-order regions such as the nucleus accumbens (NAc) (8, 61). Its connection to the vagus nerve provides a potential link for the gut microbiota to influence NTS function and downstream projection sites.

The gut microbiota has been reported to modulate neuropeptide expression, neuronal activity, and microglial activation in the NTS. CONV-R mice exhibit decreased expression of the anorexigenic neuropeptides glucagon-like peptide-1 (GLP-1) and Bdnf in the brainstem compared with GF mice (47). Since preproglucagon neurons in the NTS are the main source of GLP-1 in the brain (62, 63), this suggests that the gut microbiota modulates NTS function. Expression of c-Fos in the NTS can be induced by peripheral administration of the bacterial cell wall component lipopolysaccharide (LPS) (64) and decreased by oral butyrate administration (57), both of which are associated with reduced food intake. High-fat diet-induced (HFD-induced) shifts in the composition of the gut microbiota induce microglial activation (65, 66) and vagal afferent reorganization in the NTS, which are ameliorated by the antibiotic minocycline (65). Another brainstem nucleus that has recently been appreciated as regulating feeding is the dorsal raphe nucleus (DRN) (67, 68). GF mice show increased ΔFosB (a marker of long-term plasticity and cell activity) in the DRN compared with CONV-R mice, suggesting that the gut microbiota has effects on DRN activity (69). Whether such gut microbial modulation of the NTS and DRN actually leads to changes in feeding behavior remains to be seen and will need to be distinguished from effects on their downstream projection sites.

**Gut microbiota and non-homeostatic feeding controls**

**Cortical regions.** The prefrontal cortex (PFC), orbitofrontal cortex (OFC), and insula control motivational and rewarding aspects of

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**Table 1. Gut microbiota-mediated changes in brain regions related to homeostatic feeding behavior**

<table>
<thead>
<tr>
<th>Neurophysiological change</th>
<th>Conditions compared</th>
<th>Model organism</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothalamus</td>
<td></td>
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<tr>
<td>Altered gene expression of feeding-related neuropeptides: BDNF, NPY, AgRP, POMC, CART, SOCS-3</td>
<td>CONV-R vs. GF</td>
<td>Mice</td>
<td>47, 48</td>
</tr>
<tr>
<td>Altered proteome (neuropeptides, transmitter release, signaling pathways, synapses)</td>
<td>CONV-R vs. GF</td>
<td>Mice</td>
<td>49</td>
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<tr>
<td>Altered transcriptome (extracellular matrix function)</td>
<td>Conventionalized GF vs. GF</td>
<td>Mice</td>
<td>50</td>
</tr>
<tr>
<td>Neurotransmitter synthesis (5-HT, dopamine, BDNF) affected by gut microbial aromatic AA metabolism</td>
<td>Fetal infusion of vehicle vs. antibiotics</td>
<td>Piglets</td>
<td>51, 52</td>
</tr>
<tr>
<td>SCFAs alter c-Fos expression, reduce food intake</td>
<td>Vehicle vs. SCFA administration</td>
<td>Mice</td>
<td>55, 57</td>
</tr>
<tr>
<td>ClpB stimulates POMC neurons, reduces food intake</td>
<td>Vehicle vs. E. coli protein injection</td>
<td>Rats</td>
<td>60</td>
</tr>
<tr>
<td>Nucleus of the solitary tract</td>
<td></td>
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<tr>
<td>Altered gene expression of GLP-1 and BDNF</td>
<td>CONV-R vs. GF</td>
<td>Mice</td>
<td>47</td>
</tr>
<tr>
<td>LPS ↑ c-Fos expression</td>
<td>Vehicle vs. LPS injection</td>
<td>-</td>
<td>64</td>
</tr>
<tr>
<td>Butyrate ↓ c-Fos expression</td>
<td>Vehicle vs. oral butyrate administration</td>
<td>Mice</td>
<td>57</td>
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<tr>
<td>HFD induces microglial activation, vagal afferent reorganization</td>
<td>Low-fat diet vs. HFD</td>
<td>Rats</td>
<td>65, 66</td>
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<tr>
<td>Dorsal raphe nucleus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Altered ΔFosB activity</td>
<td>CONV-R vs. GF</td>
<td>Mice</td>
<td>69</td>
</tr>
</tbody>
</table>
social behavior is regulating myelination in the PFC, a region that plays a key role in planning and decision making (29, 81–85). Gut microbes regulate myelin gene expression and differentiation by producing metabolites such as p-cresol that could impair oligodendrocyte differentiation (82) and by affecting levels of microRNAs that target translation of myelin-related genes (85). In addition to myelin-related genes, comparison between GF and CONV-R mice reveals gut microbial regulation of genes involved in synaptic long-term potentiation (LTP), steroid hormone metabolism, citrate cycle, and cAMP-mediated signaling in the frontal cortex, hippocampus, and striatum (86). Supporting this regulation of synaptic changes, the gut microbiota also influences feeding (1). While the PFC classically inhibits impulsive feeding behavior (1, 70–73), a subset of PFC neurons promotes food intake in sated animals (74, 75). The insula (76, 77) and OFC (78, 79) integrate sensory and internal state inputs to encode the perceived value of palatable foods that then influence feeding motivation (1). Cortical regions activated by hunger show similar patterns in rodents and humans (80), suggesting that findings from rodent studies of the cortex may apply to humans.

Recent studies of social and stress-related behaviors in rodents have implicated the gut microbiota in controlling development and function of the frontal cortex, particularly the PFC (29, 81). One of the mechanisms by which gut microbiota affect

**Table 2. Gut microbiota–mediated changes in brain regions related to non-homeostatic feeding behavior**

<table>
<thead>
<tr>
<th>Neurophysiological change</th>
<th>Conditions compared</th>
<th>Model organism</th>
<th>References</th>
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<tbody>
<tr>
<td><strong>Prefrontal cortex</strong></td>
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<tr>
<td>Altered myelination</td>
<td>CONV-R vs. GF; CONV-R vs. antibiotics</td>
<td>Mice</td>
<td>82–84</td>
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<tr>
<td>Altered transcriptome (synaptic LTP, steroid hormone metabolism, citrate cycle, cAMP signaling)</td>
<td>CONV-R vs. GF</td>
<td>Mice</td>
<td>86</td>
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<tr>
<td>Altered expression of BDNF, NGFI-A, and ΔFosB</td>
<td>CONV-R vs. GF</td>
<td>Mice</td>
<td>86, 87</td>
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<tr>
<td>L. rhamnosus (↓) GABA receptor (\Delta z), reduces anxiety- and depression-related behavior</td>
<td>Vehicle vs. L. rhamnosus (JB-1) treatment</td>
<td>Mice</td>
<td>88</td>
</tr>
<tr>
<td>Altered reversal learning</td>
<td>Fecal microbiota transplant from obese vs. nonobese humans</td>
<td>Mice</td>
<td>91</td>
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<tr>
<td>Altered AA metabolism ((\alpha)-serine)</td>
<td>CONV-R vs. GF</td>
<td>Mice</td>
<td>92</td>
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<tr>
<td>Prebiotic GOS (↑) NMDA receptor subunit 1, (↑) cortical neuronal response to NMDA, improve attention</td>
<td>Control vs. prebiotic Bimuno GOS (B-GOS) water</td>
<td>Rats</td>
<td>94, 95</td>
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<td><strong>Insula</strong></td>
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<td>Resting state functional connectivity correlates with gut microbiota diversity</td>
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<td><strong>Nucleus accumbens</strong></td>
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<td>HFD (↓) insulin signaling, (↑) inflammation, induces anxiety- and depression-like behavior</td>
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<td>Prebiotic FOS after HFHS diet normalize dopamine signaling genes, reduce palatable food preference</td>
<td>FOS addition to control vs. HFHS diet</td>
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<td>Functional connectivity associated with fecal indole levels</td>
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<td>Humans</td>
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<tr>
<td>Propionate reduces activity, reduces energy intake</td>
<td>Inulin vs. inulin-propionate ester</td>
<td>Humans</td>
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<td><strong>Striatum</strong></td>
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<td>Altered dopamine turnover rate</td>
<td>CONV-R vs. CF</td>
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<td>Altered AA metabolism</td>
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<td>Altered expression of peptidoglycan-sensing proteins during development</td>
<td>CONV-R vs. GF and antibiotics</td>
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<td><strong>Ventral tegmental area</strong></td>
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<td>L. reuteri corrects synaptic plasticity</td>
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<td><strong>Hippocampus</strong></td>
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<td>Altered structure (volume, dendritic atrophy)</td>
<td>CONV-R vs. GF</td>
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<td>Altered neurogenesis</td>
<td>CONV-R vs. antibiotics; CONV-R vs. GF</td>
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<td>Defective microglial maturation and associated synaptic abnormalities</td>
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<td>Altered expression of BDNF and its receptor TrkB</td>
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<td>Altered levels of 5-HT, 5-hydroxyindoleacetic acid, GABA, γ-glutamine</td>
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<td>Prebiotic GOS and FOS (↑) BDNF, NMDA receptor subunits 1 and 2A</td>
<td>Control vs. prebiotic FOS or GOS water</td>
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<tr>
<td>L. rhamnosus (↑) GABA receptor (\Delta z), glutamate, glutamine, N-acetyl aspartate</td>
<td>Vehicle vs. L. rhamnosus (JB-1) treatment</td>
<td>Mice</td>
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<tr>
<td>Decreased memory scores</td>
<td>Fecal microbiota transplant from obese vs. nonobese humans</td>
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<td>A. muciniphila, probiotic VSL3 improve diet-induced cognitive deficits</td>
<td>Vehicle vs. probiotic supplementation to HFD-or cafeteria diet–fed mice</td>
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script levels of synaptic plasticity genes and neurotransmitter receptors. GF mice show reduced gene expression of BDNF in the PFC (87) and nerve growth factor–inducible clone A (NGFI-A) in the PFC and OFC (86), and increased expression of ΔFosB in the PFC (87), compared with CONV-R mice. Treatment of healthy CONV-R mice with *Lactobacillus rhamnosus* reduces gene expression of GABA receptor Aα2 in the PFC and reduces anxiety- and depression-related behavior in a vagal nerve–dependent manner (88). The gut microbiota may also influence the insula, as is suggested by a correlation between insular resting state functional connectivity and gut microbial diversity in humans (89).

Overall, the gut microbiota can modulate myelination and synaptic gene expression in the frontal cortex with consequent effects on social and anxiety-related behaviors. Since cortical neural networks that control social and feeding behavior are closely intertwined (90), the gut microbiota may have the potential to influence feeding behavior through cortical regulation.

Although a causal link between gut microbiota and cortical regulation of feeding behavior remains to be established, a few studies suggest that one potential mechanism may involve gut microbial amino acid metabolism. Deficits in inhibitory control, which are mediated by the PFC, may contribute to unhealthy eating and exercise habits in obesity. Inhibitory control is associated with obesity-dependent alterations in gut bacterial one-carbon and aromatic amino acid metabolic pathways in human cohorts (91). Furthermore, fecal microbiota transplant from obese individuals is sufficient to alter reversal learning and medial PFC gene expression in recipient mice (91). This study suggests that the gut microbiota may modulate a cognitive function involved in feeding via the PFC. Another study shows that gut microbes regulate amino acid metabolism in various brain regions, including decreased cortical d-serine in CONV-R compared with GF mice (92). d-serine acts as a coagonist with glutamate on NMDA receptors (93). Prebiotic supplementation with galacto-oligosaccharides (GOS), which induces gut microbiota proliferation, increases protein expression of NMDA subunit 1 and levels of d-serine in the frontal cortex, enhances cortical neuronal responses to NMDA, and improves cognitive performance in rats (94, 95). Because NMDA receptors and d-serine have been implicated in control of appetite, food preference, and reinforcement learning (93, 96, 97), gut microbial influence on this system in the frontal cortex could potentially alter host feeding behavior. Future studies investigating the effects of altering microbial amino acid metabolism in the PFC via microbiota transplant or prebiotics on host food intake and preference are necessary.

*Mesolimbic dopamine pathway*. The mesolimbic dopamine pathway, from the ventral tegmental area (VTA) to the NAc locat-
ed in the ventral striatum, encodes food-associated reward, which can override homeostatic signals to promote excessive consumption (1, 6, 70, 98–100). Both the VTA and the NAc are modulated by homeostatic information from the hypothalamus (98, 101) and gut hormones (1, 102). Growing evidence suggests that the gut microbiota also regulates the mesolimbic pathway by modifying dopaminergic transmission with potential effects on reward-associated behavior (103, 104). One study showed that GF rats have a lower dopamine turnover rate in the striatum than CONV-R rats (105), while another study reported that GF mice have higher dopamine, 5-HT, and noradrenaline turnover rates in the striatum than CONV-R mice (86). This difference may be explained by differences in rodent species and strain, but they nevertheless implicate a role for gut microbiota in dopamine metabolism. One potential mechanism by which the gut microbiota affects neurotransmitter levels is through the modification of amino acid metabolism (92, 106). Predicted increases in a bacterial enzyme for the synthesis of the dopamine precursor phenylalanine correlate with decreased ventral striatal functional MRI (fMRI) responses during reward anticipation in humans, suggesting a link between gut microbial metabolism and behavior (106).

In addition to dopamine itself, the gut microbiota also affects dopamine receptor expression and other synaptic proteins. GF mice show significantly higher protein expression of synaptophysin and PSD-95 than CONV-R mice (86). Gut microbiota composition also correlates with increases in striatal gene expression of dopamine D1 receptor, decreases in striatal expression of dopamine D2 receptor, and changes in impulsivity measures in a rat model of alcohol seeking (107).

The gut microbiota can also influence host behavior through mesolimbic structures. Treatment of maternal HFD offspring or autism mouse models with *Lactobacillus reuteri* corrects social deficits by rescuing social interaction–induced synaptic plasticity in the VTA in a vagal nerve–dependent manner (108, 109). Changes in gut microbiota are associated with anxiety- and depression-like behavior in mice with diet-induced obesity through decreased insulin signaling and increased inflammation in the NAc and amygdala, which can be transferred to GF mice by fecal transplant and improved by antibiotic treatment (110). Relevant to feeding behavior, prebiotic supplementation with fructo-oligosaccharides (FOS), which alters gut microbiota composition, can modify motivation to eat a high-fat, high-sugar (HFHS) diet in mice. When mice are fed FOS after chronic HFHS exposure, they show decreased palatable food tropism and consumption, associated with normalization of NAc expression of genes involved in dopamine signaling (111).

Despite these associations between gut microbiota, mesolimbic physiological changes, and behavior, the underlying mechanisms of gut microbial regulation of the mesolimbic pathway remain unclear. However, some studies have suggested that bacterial molecules can act directly or indirectly on the striatum. In mice, the developing striatum expresses proteins that detect the bacterial cell wall component peptidoglycan, and their expression is sensitive to gut microbiota depletion, suggesting that the gut microbiota modifies striatal development via peptidoglycan (112). In humans, indole metabolites and propionate may alter mesolimbic activity through indirect gastrointestinal or vagal pathways (113, 114). Fecal levels of indole metabolites strongly associate with functional connectivity of the NAc, potentially interacting with GLP1–producing enteroendocrine L cells or serotonergic enterochromaffin cells to act on vagal afferents that then communicate with central reward regions (113). Increasing colonic propionate levels in humans reduce activity in the NAc and caudate nucleus, which correlates with a decrease in subjective appeal of high-energy food pictures and in energy intake during an ad libitum meal (114). Thus, studies in both rodents and humans suggest a relationship between the gut microbiota and mesolimbic dopamine pathway in modulating feeding behavior (111, 114) through gene expression changes and metabolites such as propionate and indoles. Future studies are needed to elucidate the neural pathways by which these metabolites affect feeding behavior and to identify candidate metabolites that can impact the VTA in addition to the NAc.

**Hippocampus.** The hippocampus regulates food intake by integrating information about the external visuospatial environment, meal-related memories, learned experiences, and energy status (1, 115, 116). The ventral subregion (vHP) helps consolidate feeding-related learned associations by sensing endocrine signals and projecting to higher brain regions including the PFC and NAc (1, 117). Higher body mass index correlates with reduced hippocampal volume, suggesting that hippocampal dysregulation may contribute to obesity (118–120). The gut microbiota affects many aspects of hippocampal physiology, including structure, neurogenesis, gene expression, and neurochemistry (29). In mice, the gut microbiota is required to maintain hippocampal structure, with GF mice showing increased CA2/3 volume and dendritic atrophy of vHP pyramidal neurons compared with CONV-R mice (121). Supporting this notion in humans, increases in taxonomic diversity of the gut microbiota correlate with sparing of hippocampal microstructure (46). The gut microbiota (29) and dietary changes (122) also affect hippocampal neurogenesis, which is important for maintenance of spatial memory and learning capacity (122). One study found that broad-spectrum antibiotic treatment of CONV-R mice decreases neurogenesis in the subgranular zone of the dentate gyrus, which could be ameliorated by postnatal treatment with the probiotic VSL3, which comprises a mixture of several commensal bacterial species (123). Another study found that GF mice show increased neurogenesis in the dorsal hippocampus compared with CONV-R mice, which could not be corrected by postnatal conventionalization (124). This difference may be explained by physiological differences between GF rearing and postnatal antibiotic treatment (29). Furthermore, the gut microbiota affect microglia, which are important for brain development including synaptic pruning and remodeling throughout adulthood (125). GF mice show defective microglial maturation and decreased reactivity in the hippocampus compared with CONV-R or conventionalized GF mice (125, 126), associated with abnormally increased synaptic density and decreased neuronal firing rate (126). Microglial abnormalities are corrected by recolonization with complex microbiota (125, 126), SCFAs (125), and a limited consortium of *Bifidobacterium* species (126), suggesting that specific microbes and metabolites can regulate microglial homeostasis and, consequently, synaptic function.

In addition to altering synaptic function, the gut microbiota influences expression of synapse-related genes in the hippocamp-
Conventionalized GF mice show downregulation of genes involved in LTP compared with GF mice (126). GF (R8) and antibiotic-treated mice (127) also exhibit decreased hippocampal expression of BDNF and its receptor TrkB (128) compared with CONV-R mice. Gut microbiota may also impact neurotransmitter levels: GF mice display increased levels of hippocampal 5-HT and its metabolite 5-hydroxyindoleacetic acid (129) and decreased levels of GABA and L-glutamine (92) in the hippocampus. Prebiotic and probiotic treatments alter levels of neurotransmitters and their receptors, supporting their regulation by gut microbes. Prebiotic treatment with FOS and GOS increases hippocampal gene and protein expression of BDNF and NMDA receptor subunits 1 and 2A (94). Treatment of healthy CONV-R mice with L. rhamnosus increases gene expression of GABA receptor A2 in the hippocampus (88) and increases hippocampal glutamate, glutamine, and N-acetyl aspartate levels (130).

These neurophysiological changes may contribute to influences of the gut on hippocampus-dependent learning and memory (29, 131). While causal effects of the gut microbiota on hippocampal feeding regulation remain to be proven, the assays used in rodent models of microbiota depletion or probiotic treatment—novel object recognition, Barnes maze, and Morris water maze—suggest it is possible. Antibiotic (29) and probiotic treatments (29, 131) modulate spatial memory in mice, as measured in the Barnes maze and Morris water maze (132). Spatial memory is an important component of food-place memory, which is encoded by hippocampal dopamine 2 receptor (hD2R) neurons that regulate food intake (116). GF, antibiotic-treated, and probiotic-treated mice also show altered behavior in the novel object recognition test, which tests working memory but may also hint at contextual memory (133). Episodic memory, which involves “what-where-when” experiences, significantly affects food intake in human studies (115) and can be evaluated in mice using object-place-context tests (134, 135). Future studies are needed to establish a causal connection between gut microbiota and hippocampal feeding-related functions, including tests for food-specific episodic (134, 135) and food-place (116) memory in microbiota-depleted or probiotic-treated mice. Profiling hD2R neurons (116) in microbiota-depleted compared with CONV-R mice would also be of interest.

Supporting this potential role of the gut microbiota in regulating feeding-related memory, a few recent studies have reported links between gut microbes and diet-induced and obesity-associated memory deficits (136–138). Gut microbiota composition and plasma and fecal levels of AAAs are associated with short-term and working memory in humans with obesity (136). Fecal microbiota transplantation from obese individuals leads to decreased memory scores in recipient mice in comparison with nonobese donors (136). In another study, early-life HFD impairs hippocampus-dependent contextual and spatial learning and memory in mice by altering the gut microbiota, specifically by depleting Akkermansia muciniphila (137). Fecal transplantation and LPS treatment are sufficient to confer these memory deficits to chow-fed mice, suggesting a causal role of the gut microbiota (137). Furthermore, treatment of HFD-fed mice with A. muciniphila ameliorates these memory deficits along with hippocampal neuronal development and LTP (137). HFD-induced memory deficits and hippocampal gene expression changes can also be prevented by probiotic treatment with VSL3 in rats (138). Together, these studies indicate the potential for specific microbes to affect hippocampal function and memory in obesity, in which cognitive deficits could predispose individuals to overeating (136). Future studies are needed to elucidate the neural mechanisms underlying gut microbial influences on hippocampal function in obesity, which may have therapeutic implications.

**Gut microbiota and vagal nerve**

The vagus nerve controls food intake by relaying chemosensory and mechanosensory information from the gastrointestinal tract to the brain to convey feeding-related signals (7–10, 139). Vagal afferent neurons expressing GPR65 extend to intestinal villi and respond to intestinal nutrients in mice (140). A subset of enterodocrine cells directly sense nutrient and other chemical stimuli, and quickly transduce these gut luminal signals to vagal neurons through glutamatergic and serotonergic synapses (141, 142). Mechanosensing vagal afferents expressing GLP-1 receptor extend axons to the muscle layers to sense gastrointestinal stretch (140, 143). Interestingly, a recent study found that activation of mechanosensing vagal neurons, rather than nutrient-sensing ones, suppresses food intake through inhibition of hypothalamic AgRP neurons (143) and through parabrachial prodynorphin neurons (144); however, the contribution of chemosensory to feeding control has not been excluded (8). Moreover, the effect of GPR65+ vagal afferents on behavior remains unknown (139). In addition to chemosensory and mechanosensory information, intact vagal signaling is required to facilitate actions of hormonal satiety signals, particularly cholecystokinin (CCK), on feeding behavior (7, 9, 139). Although it classically participates in negative feedback control of food intake (9), recent studies have revealed new roles for the vagus nerve in stimulating feeding and learning nutrient preferences through neural pathways involving the NTS and downstream projection sites.

Vagal afferent neurons first terminate in the NTS, located in the brainstem (7). NTS neurons coexpressing NPY and epinephrine that receive vagal afferents stimulate feeding, showing an orexigenic role for the vagus nerve (145). The vagus nerve also forms multisynaptic pathways via the NTS to higher-order brain regions (61) involved in non-homeostatic feeding controls, such as the striatum (146, 147) and hippocampus (148, 149), and mediates brain functions in mice. Vagal activation induces dopamine release from the substantia nigra and conditions flavor and place preference (146). Vagal neurons, specifically those expressing CCK receptors, are also necessary for hippocampus-dependent episodic and spatial memory (148) and influence hippocampal neurogenesis (148, 149). Consistent with its effects on reward and memory, the vagus nerve has recently been appreciated as modulating nutrient preference learning (10, 150). Vagal nerve signaling is key to developing preference for sugar over artificial sweetener independent of taste in mice (151, 152) through activation of caudal NTS (151) and dopaminergic VTA neurons (152). Both vagal innervation and duodenal sensing are also required for preference learning for fats and proteins in mice (153). Although all these studies were conducted in rodents, evidence from gastric bypass surgeries and nerve stimulation suggests that the vagus nerve may also play a role in food intake control in humans (150).
Overall, the vagus nerve plays essential roles in both homeostatic and non-homeostatic feeding behavior by modulating appetite and nutrient preference learning. Owing to its proximity to the gut microbiota in the gastrointestinal lumen, it serves as an appealing potential pathway by which gut microbes may affect host feeding behavior that warrants further investigation. Vagal neurons express numerous G protein-coupled receptors (GPCRs) (154, 155), and can be subclassified based on their expression of receptor-encoding genes Gpr65, Htr3a/b, Piezo1, Nsr1, Cyslt2, Gpr174, and Sipr3 (154). Intestinal GPR65+ vagal neurons also express Gpr35, Cbr1 (encoding carbonyl reductase 1), Gpr149, Gpr161, and Cbr2 (encoding corticotropin-releasing hormone 2) (155). Gut microbial metabolites can interact with some of these GPCRs based on evidence from high-throughput screening of microbial ligand-receptor binding (156, 157). Of the aforementioned receptors, metabolomes modulated by the human gut microbiota are predicted to affect Nsr1, Sipr3, Gpr35, Gpr149, and Gpr174 (156). GPR35 binds aromatic, acidic metabolites such as the tryptophan metabolite kynurenic acid (155), which is modulated by gut microbes (158). SIPR3 binds sphingolipids, which are also produced and modulated by gut microbes (159). PIEZO1 channels have also been reported to bind fecal RNA potentially derived from gut microbes (160). In addition to direct activation of receptors on vagal neurons, gut luminal microbial metabolites such as butyrate, isobutyrate, and isovalerate may also bind receptors on enterochromaffin cells, stimulating the release of secondary metabolites that activate vagal afferents (142).

Some mechanisms by which microbial metabolites can interact with enteroendocrine cells and vagal neurons to alter feeding behavior have been reported to involve SCFAs, bile acids, and indoles (20, 161). SCFAs can act directly on vagal neurons, which express the SCFA receptor FFAR3 (also called GPR41) (156, 162), to control food intake. Intraportioneal injection of SCFAs, especially butyrate, reduces food intake in fasted mice, which is attenuated by hepatic vagotomy and by capsaicin-induced sensory denervation (163). Furthermore, butyrate injection induces cellular activation markers in the nodose ganglion and medial NTS and can activate intracellular calcium signaling in vagal neurons ex vivo (163). SCFAs can also affect nutrient sensing and hormone production by enteroendocrine cells to indirectly affect vagal signaling. Treatment of enteroendocrine cell cultures with propionate and butyrate increases mRNA levels of umami taste receptors, suggesting that SCFAs can alter enteroendocrine sensitivity to nutrients (164). Propionate can also induce GLP-1 secretion by enteroendocrine L cells and colonic crypts via the receptor FFAR2 (also called GPR43) (165-167). Similarly, indole (168) and bile acids (162, 169) can also induce GLP-1 production by enteroendocrine cells, which then stimulates colonic vagal afferents (168).

Aside from metabolites, vagal neurons may interact with bacterial components, namely LPS via TLR4 receptors. Chronic LPS treatment leads to reduced satiation and hyperphagia in rats by inhibiting vagal leptin signaling that results in CCK resistance (170-173). HFD-driven gut microbiota dysbiosis and inflammation, including increased serum LPS levels, are also associated with vagal remodeling — withdrawal of vagal afferents from the gut and NTS and microglial activation at the nodose ganglion — which is ameliorated by antibiotic treatment (65, 170, 174). These findings suggest that endotoxemia can contribute to the development of obesity via the vagus nerve. In summary, the vagus nerve serves as a likely pathway for gut microbes to modulate host feeding behavior through direct receptor activation or indirect interactions with enteroendocrine cells (Figure 2). Future studies are needed to better understand mechanisms by which the gut microbiota interacts with the vagus nerve, particularly identifying microbial ligands for orphan GPCRs and discovering the downstream effects of activating those receptors. Studies testing effects of vagal receptor activation by microbial ligands on feeding behavior are also needed in addition to current vagal ablation strategies. This understanding could contribute to developing microbiota-based vagal modulation strategies to treat obesity and eating disorders, which may refine and extend existing electrical interventions (175).

Conclusion
An increasing number of studies together suggest that the gut microbiota affects the structure and function of neural pathways that play important roles in regulating both homeostatic and non-homeostatic feeding behaviors. However, these studies largely use bulk depletion of the microbiota in animal models to provide proof-of-concept that an intact microbiota is required to maintain an aspect of gene expression, biochemical profile, or neurophysiology. More studies are needed to determine which of these findings are reproducible across different animal models and microbiota paradigms, and to provide more rigorous evidence that the microbiota affects feeding-related neural circuits. Further, integrative studies are necessary to determine whether observed changes in relevant neural circuits actually render downstream alterations in host feeding behavior. If so, detailed understanding of specific microbial functions and signaling pathways across the gut-brain axis would be needed to dissect underlying signaling mechanisms. There remains a knowledge gap in microbial effects on specific subtypes of brain neurons compared with neurons of the vagus nerve. Recent advances in single-cell sequencing (176) may serve as a launching point for future studies on gut microbiota and neuronal subtypes in obesity. Corresponding human studies that manipulate specific microbes and metabolites will be important for assessing host-microbe interactions that occur in humans and their potential relevance to metabolic and eating disorders. Understanding the influence of the gut microbiota on homeostatic and non-homeostatic feeding behaviors may reveal novel insights into the biological underpinnings of food choice, with the potential to inform new approaches for modifying food preferences in obesity and eating disorders (177).

Acknowledgments
KBY is supported by funds from the UCLA Whitcome Fellowship. EYH is supported by funds from the Army Research Office Multidisciplinary University Research Initiative (W911NF-17-0402) and Chan Zuckerberg Initiative (2018-191860); is a New York Stem Cell Foundation Robertson Investigator; and is supported in part by the New York Stem Cell Foundation. Address correspondence to: Kristie B. Yu or Elaine Y. Hsiao, Department of Integrative Biology & Physiology, 610 Charles E. Young Drive East, University of California, Los Angeles, California 90095, USA. Email: kristie.yu15@gmail.com (KBY). Email: hhsiao@g.ucla.edu (EYH).


The Journal of Clinical Investigation

140. de Lartrigue G, et al. Leptin resistance in vagal afferent neurons inhibits cholecystokinin signal-


