Gut microbial molecules in behavioural and neurodegenerative conditions

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Abstract | Mounting evidence suggests that the gut microbiome impacts brain development and function. Gut–brain connections may be mediated by an assortment of microbial molecules that are produced in the gastrointestinal tract, which can subsequently permeate many organs, including sometimes the brain. Studies in animal models have identified molecular cues propagated from intestinal bacteria to the brain that can affect neurological function and/or neurodevelopmental and neurodegenerative conditions. Herein, we describe bacterial metabolites with known or suspected neuromodulatory activity, define mechanisms of signalling pathways from the gut microbiota to the brain and discuss direct effects that gut bacterial molecules are likely exerting on specific brain cells. Many discoveries are recent, and the findings described in this Perspective are largely novel and yet to be extensively validated. However, expanding research into the dynamic molecular communications between gut microorganisms and the CNS continues to uncover critical and previously unappreciated clues in understanding the pathophysiology of behavioural, psychiatric and neurodegenerative diseases.

Gut microbiome–brain interactions

Decades passed before the principles of microbial pathogenesis took root after Louis Pasteur originally proposed a bacterial aetiology for infectious disease in the 1850s. Similarly, the pursuit of mechanistic evidence explaining the connections between intestinal bacteria and neurological disease has taken a century of research since hypothesized by Elie Metchnikoff and others in the early 1900s. The gut microbiota comprises bacteria and other microorganisms, including viruses, fungi, protists and archaea, that permanently or transiently inhabit the lower gastrointestinal tract, especially the small intestine and colon[1]. The colon, in particular, is densely populated and teeming with dynamic metabolic activity, with a constant bidirectional flux of molecules between the microorganism and the host that extends beyond the gut into the entire body[2,3]. This chemical 'factory' can affect the maternal environment during pregnancy and prenatally exposes the fetus to signals of microbial influence[4]. After birth, the gut microbiota is quickly established and the community then stabilizes within the first 2 years of life[1], leading to lifelong and intimate crosstalk between the host and their microbial co-inhabitants. The level of diversity and the specific members of the microbiota can differ greatly between individuals and can shift within an individual depending on age, genetics, health status, diet and lifestyle[5].

The gastrointestinal tract contains many diverse cell types in close proximity and is exposed on the luminal side to an external environment containing the dietary components and the gut microbiota. Within the gut tissue exist about 70% of the body's immune cells constantly sampling microbial components and maintaining homeostasis[6], along with dense innervation along the gut by neurons that are housed entirely within intestinal tissue (10^8 intrinsic neurons[7]) as well as neurons connecting the gut to the spinal cord and brain. The vagus nerve, a principle neuronal connection between the gut and the brain, comprises a bundle of neurons that send and receive signals directly between gut tissue (and other organs) and the brainstem. These signals can then be further transmitted throughout the brain.

Evidence that the gut microbiota influences brain development and function began to emerge with studies comparing conventionally colonized mice (also called specific pathogen-free mice) against mice in drastically altered microbial states, such as the complete absence of microbial exposure (germ-free mice). Additional insights were gained by using controlled introduction of a certain microorganism or community (gnotobiotic mice), or by treating conventional mice with broad-spectrum antibiotic cocktails that depleted their microbiome. Germ-free and antibiotic-treated animals exhibit altered levels of neurotrophic factors such as brain-derived neurotropic factor (BDNF) as well as abnormal neuropeptide and neurotransmitter levels[8–13], all of which can, in turn, affect crucial neurodevelopmental processes such as neurogenesis, synaptogenesis and synaptic maturation and pruning, and neural activity[8,9,14–17]. Gross morphology and volume of the brain also differs between specific pathogen-free and germ-free mice, especially in the amygdala, hippocampus and thalamus regions[18,19], with morphological changes observed at the cellular level in various cell types, including neurons, oligodendrocytes and microglia, in both germ-free and antibiotic conditions[12,18,20,21]. Microbial exposure also alters the host neurological status and leads to changes in signalling pathways. For instance, the hypothalamic–pituitary–adrenal axis is dysregulated in germ-free and antibiotic-treated mice[14], which results in an exaggerated glucocorticoid response. These hypothalamic–pituitary–adrenal axis changes are associated with some behavioural patterns in testing paradigms that model social activity[22–24], anxiety[9,25,26], cognitive function and depressive[25,27] behaviours[10,11,24,28–30].

Gut microbial communities differ between individuals with certain health issues and healthy controls[31]. An imbalance in the gut microbial community is associated with various neurological and psychological disorders, although establishing which of these associations are causal relationships remains under investigation[32–38] (FIG. 1). Recent work has shown that an altered

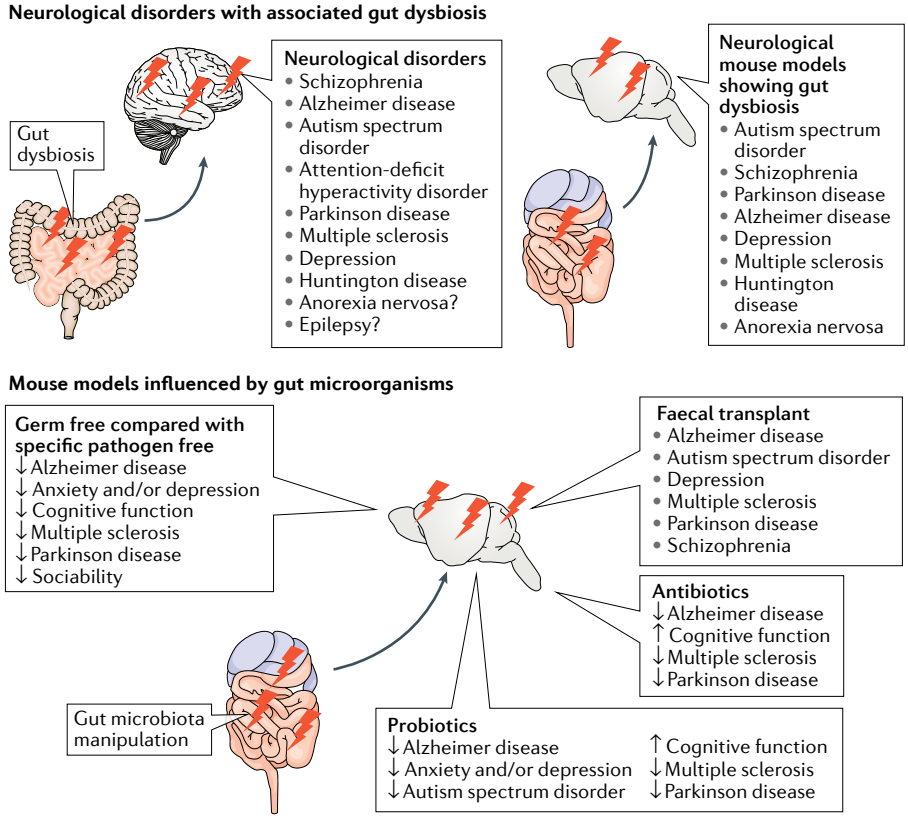


Fig. 1 | **Neurological disorders and models associated with shifts in gut microbiota.** Top: human conditions and mouse models with known differences in the gut microbial community compared with healthy controls. Question marks show disorders with implicated but less established changes to the microbiota. Bottom: rodent models shown to be improved, exacerbated or caused by manipulation of gut microorganisms. These are divided into four categories of experimental strategy, including the study of germ-free versus specific pathogen-free mice, colonization conditions, probiotic bacteria administration, faecal microbial transplant or antibiotic treatment. Up or down arrows indicate a respective increase or decrease in listed disease or function following microbial manipulation in the germ-free, probiotic or antibiotic state. Note that subtle variations in experimental methodology in faecal transplant studies mean that the effects shown here are likely to be an oversimplification (for example, transfer could be made from a donor mouse or human, from a control or symptomatic animal or individual and/or into a wild-type or a disease model recipient).

gut microbiota is sufficient to exacerbate neurological and psychological symptoms in some mouse models of multiple sclerosis[39], Parkinson disease[40], Alzheimer disease[41], depression[42], schizophrenia[33], attention-deficit hyperactivity disorder[43] and, possibly, autism spectrum disorder (ASD)[44]. These studies are accomplished through the use of faecal microbial transplantation, whereby the faecal microbiota from human donors or other mouse models is used to colonize germ-free mice, limiting the confounding variables typical to human studies by using well-controlled, albeit reductionist, preclinical systems[45]. Although these provocative studies are exciting, conclusions drawn from a small number of human donors remain speculative unless they are reproduced in larger cohorts of patients. In addition, causal inferences from human–murine microbiota transfer studies are limited by inter-species differences in both microbiology and neurobiology[45]. More established bacterial manipulations, such as treatment with particular bacteria or depletion of bacteria with antibiotics, have been shown to ameliorate disease symptoms in mouse models of ASD[46,47], multiple sclerosis[48–50], anxiety and depression[15,51–53], cognitive defects[54,55] and Parkinson disease[40], as well as in humans with ASD[56,57], multiple sclerosis[58], anxiety and depression[59–62]. Some of the effects of bacterial treatments on human brain activity have been characterized by changes observed in functional magnetic resonance imaging[63,64]. Thus, emerging evidence suggests that neurological states may be impacted by gut microorganisms and their by-products.

Various associations between altered microbiome profiles and diseases of the brain have been described, and the contribution of microbial communities or particular bacterial species to behaviour, cognition and neurodegeneration is continually being established[65]. Furthermore, the gut microbiome harbours astonishing genetic diversity, with more than 22 million genes sequenced from human gut microbial populations, and an immense pool of unique enzymes capable of producing and modifying a wide array of chemical structural groups[66]. We build on these foundational discoveries to describe and conceptualize how decoding of chemical messages that mediate the observed effects of the gut–brain axis provides promise in both understanding and treating a number of neurologic diseases. The following sections will delineate categories by source of the precursor (de novo bacterial, host or diet-derived sources) that can be transformed by gut bacteria and the bioactive molecules that result from microbial metabolism (FIG. 2). Brief descriptions of the effects of specific molecules are also provided.

Production of bacterial molecules

Microorganisms produce many proteins, vitamins and structural components that can serve to benefit or negatively affect the host. Many of these are generated via multistep biosynthetic pathways otherwise absent in mammals[67]. These molecules sustain bacterial functions, such as signalling, structural components and energy sources, although some, such as proteinaceous toxins, are mainly known for their roles affecting host systems.

Microorganism-associated molecular patterns. Microorganism-associated molecular patterns (MAMPs) are well-conserved components of microbial cells, and they are acutely detected by the host throughout the body, including the brain[68]. MAMPs play crucial roles in structural integrity and basic function for all classes of microorganisms and are complex molecules comprising diverse chemical groups including nucleotides, lipids, carbohydrates and peptides[69]. The absence of MAMPs in germ-free mice leads to incomplete immune and neurodevelopment, but their presence can induce acute or chronic inflammation associated with various neurological disorders if the host response to MAMPs remains elevated or unchecked[70]. Two principle cellular surface component MAMPs that appear to be sufficient to

alter brain development and function are peptidoglycan and lipopolysaccharide (LPS). Peptidoglycan, a structural component of almost all bacterial cell walls, was recently shown to be translocated into the developing brain, affecting gene expression and social behaviour[71]. LPS, another ubiquitous surface molecule of Gram-negative bacteria, has been detected co-localizing with its receptor in rat brains[72]. LPS injection induces sickness behaviour[73], cognitive impairment[74] and acute depressive-like behaviours in mice[75] and affects fetal brain development[76,77]. Additionally, chronic or acute exposure to MAMPs is used to promote disease-related symptoms in models of ASD, depression, Parkinson disease and synucleinopathy[78–80]. These conserved microbial molecules may regulate mammalian behaviour through immune-mediated pathways via direct sensing by receptors expressed in the brain or activation of systemic inflammation and cytokine production, which can lead to altered neurological function and neuronal stress or cell death[81]. The presence, structure and immunomodulatory activity of MAMPs vary between species of bacteria, and shifts in the gut community could, therefore, affect the level of exposure and response of the host to particular MAMPs, which in turn can influence downstream health status and behaviour.

Toxins. Proteinaceous toxins produced by some bacteria exert negative effects on the host nervous system. These toxins are often similar in general structure, with multiple subunits that activate cell-surface or intracellular receptors, and can be produced by opportunistic pathogens that may reside in the commensal community for long periods of time without causing overt disease in the gut or the brain[82]. Several species of *Clostridia* are known to produce many toxins, such as lethal toxin, toxin B, epsilon toxin and enterotoxin, that can reach the brain through the systemic circulation, disrupt and cross the blood–brain barrier (BBB), inhibit neurotransmitter release and/or decrease neuron viability in targets ranging from the gut to the hippocampus[82–86]. *Staphylococcus* spp. and *Bacillus* spp. produce toxins, staphylococcal enterotoxins and cereulide, that stimulate the vagus nerve, sending signals to the brain and inducing vomiting and sickness behaviour[87–89]. Other species, such as *Salmonella* spp. and *Escherichia* spp., produce a class of proteins called amyloids, which aggregate in the intestine and may spread to the brain with a prion-like disease pattern and may contribute to neurodegeneration, such as in Parkinson disease and Alzheimer disease[90–93].

Transformation of host metabolites

Constant metabolic flux is sustained across the intestinal epithelial barrier as nutrients are absorbed and waste is secreted. The microbiota is exposed to and chemically interacts with many host molecules. The two classes of host-derived metabolites with the most evidence for gut–brain interactions are bile acids and steroid hormones.

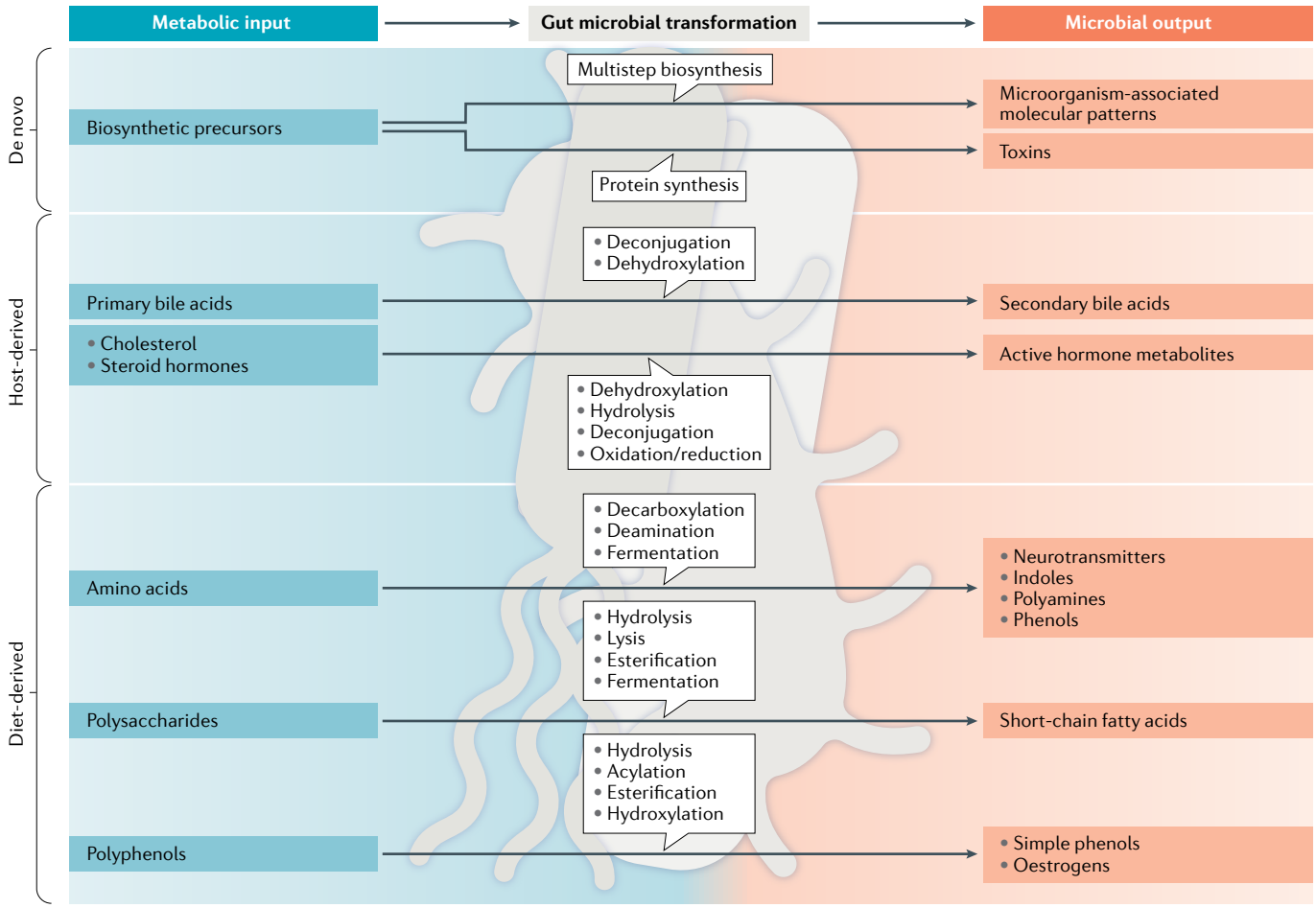


Fig. 2 | **Gut bacterial metabolites.** The modification of various substrates by the gut microbiota is shown broken down into three categories (left) of de novo bacterial, host-derived or dietary molecules. These substrates (metabolic input, shown in blue) are metabolized by many chemical processes by the microbiota (general examples are shown in white boxes). Many of the resulting metabolites have been shown to affect the brain (shown in red).

Bile acids. Primary bile acids are products of host cholesterol metabolism that play a major role in fat digestion and signalling in energy metabolism, even in the brain[94–97]. Circulating bile acids can cross the BBB and may act directly on their receptors in the brain, or have a more indirect effect by activating gut receptors, leading to the release of signals such as fibroblast growth factor and glucagon-like peptide 1, which can influence neuronal activity in multiple brain regions or the vagus nerve[98]. The most common primary bile acids are cholic acid and chenodeoxycholic acid, and these are often conjugated with the amino acid glycine or taurine[99]. Many gut bacterial species help maintain cholesterol homeostasis by modifying primary bile acids into secondary bile acids through dehydroxylation by dehydratase enzymes, deconjugation of the amino acid groups with bile salt hydrolases and further degradation with other enzymatic machinery[99,100]. Bacterial modification changes the signalling of bile acids on membrane and nuclear receptors, and alters their solubility and circulation[94]. Regulation of the presence and clearance of bile acids is involved in proper brain function, as defects in these pathways lead to many neurological phenotypes in mice and humans, such as demyelination, motor dysfunction, neuroinflammation, seizures and learning impairment[96,101–112]. Bacterial influences on bile acid conjugation and levels may be influencing these brain phenotypes. For instance, alterations in bacterial-associated bile acid levels have been observed in human and mouse model studies of Parkinson disease[113], Alzheimer disease[114,115], multiple sclerosis[116,117], alcohol dependency[118] and ASD[119], and bile acids are known to affect the hypothalamic–pituitary–adrenal axis[111,112,120]. In fact, all secondary bile acids produced by bacteria are detected in the brain of patients with Alzheimer disease, and increased ratios of secondary bile acids are correlated with their cognitive impairment and changes in brain imaging[114,115]. Some bile acids are even used as potential treatments for neurological issues such as amyotrophic lateral sclerosis and stroke[108,121,122]. The presence of bacteria in the gut changes host-wide bile acid levels, and community changes in the gut microbiota influence the levels and properties of bile acids[123–129]. These changes could be advantageous or detrimental. The most mechanistic link known between microbial metabolism of bile acids and potential neurological function may be that levels of deoxycholic acid directly increased by the microbiota are sufficient to induce production of the major neurotransmitter, serotonin, in gut enterochromaffin cells[130]. Gut serotonin levels may affect brain function in ways that are yet unknown, as hippocampal levels of serotonin are affected by the microbiota in mice, but any possible further links between gut and brain serotonin levels are not clear[8]. Cause and effect relationships between microbial manipulation of bile acids and brain function remain to be clearly defined.

Steroid hormones. Steroid hormone signalling is crucial for proper brain structure development, cognition, memory, decision-making and sexual behaviours, as well as playing a role in protection from social isolation and depression-like phenotypes[131–137]. Up to 15% of some of these hormones produced daily are detectable in the gut, as they circulate through the body, bringing them into contact with the microbiota[138,139]. The gut microbiota can influence levels of some hormones by shifting the ratio of active and inactive steroid levels through different degradation and activation pathways[140–142]. The two best-studied classes for which this is the case are androgens and oestrogens. In many cases, hormones can be conjugated for excretion, and bacteria can remove the conjugation group with hydrolytic enzymes such as β-glucuronidases (GUSs) and β-glucosidases, which reactivate the molecule for continued circulation and activity[143–146]. Members of the microbiota can also convert cholesterol to androgens[147,148], activate pro-androgens[149,150] and metabolize testosterone into other potent androgens[151,152]. Oestrogens are broken down in oxidative and reductive reactions in human faecal samples[144,153–155]. In fact, the term 'estrobolome' has been coined to describe the large collection of enteric bacterial genes capable of metabolizing oestrogens[156]. Shifts in the gut microbiota and steroid hormone levels are associated with each other in postmenopausal women[157,158] but, although the potential capacity for microbial metabolism of host hormones is vast, direct effects on brain function remain largely untested. If microbially influenced oestrogens do have direct neurological effects, they are likely neuroprotective, as oestrogens have anti-inflammatory effects on microglia[159], and lowered levels of oestrogens due to altered microbial communities appear to increase cognitive impairment and chronic inflammation[160,161]. Microorganisms may be sufficient for these phenotypes, as some steroid hormone levels can be transferred by microbial faecal transplant between mice[162], but further work is required to directly link hormone metabolites produced by the gut microbiota to neurological disease.

Transformation of dietary metabolites

The composition of the gut microbiota is heavily dependent on the dietary input of the host[3,163]. The frequency of meals and types of foods influence the quantity of substrates metabolized by bacteria, which bacterial species wax and wane in abundance and, ultimately, the type and amount of downstream bacterial metabolites that are produced. Further, significant evidence shows that microbial metabolites of amino acids, complex plant polysaccharides and polyphenols exert an influence on the brain.

Amino acids. Microorganisms encode genetic machinery to produce many amino acids, some of which can contribute to circulating host levels[164,165]. However, it is more likely that any microbial influence on the CNS via amino acid levels occurs through modification of dietary amino acids by deamination and decarboxylation pathways. The by-products of bacterial amino acid metabolism include ammonia, short-chain fatty acids (SCFAs), simple phenols, indole derivatives, neurotransmitters, organic acids, gaseous compounds and amines. Those most likely to affect brain function are described below.

Gut bacteria encode multiple gene pathways that metabolize the aromatic amino acids tyrosine, phenylalanine and tryptophan into a large group of downstream products, many of which are neurotransmitters[166,167]. Tyrosine is metabolized to tyramine and then into two catecholamines, dopamine and noradrenaline. Tyramine in the intestine of germ-free mice also induces the production of serotonin[130]. Noradrenaline is produced by gut bacteria[12,168], but it is not well understood how[168]. However, multiple bacteria have been shown to synthesize noradrenaline up to the millimolar range in vitro[169,170]. Catecholamine production by the microbiota may be sufficient for behavioural alterations, as mice treated with antibiotics were more sensitive to the dopamine signalling and behavioural effects of cocaine[171]. Whether these neuroactive molecules influence the local enteric nervous system or can affect the brain, even indirectly, is an active area of study.

Tryptophan is broken down by the microbiota into indole derivatives and also tryptamine and kynurenine metabolites, all of which have neuroactive

properties[172–174]. Some of these seem to only be produced by the microbiota, as they are undetectable in germ-free mice until bacterial colonization[166,167]. Many of these can cross the BBB, and thus circulating tryptophan metabolites originating in the gut can contribute to levels in the brain[175]. Indole derivatives such as indolepropionic acid have antioxidant properties, making this an attractive target for Alzheimer disease, whereas others such as indoxyl sulfate induce neuroinflammation in models of chronic kidney disease[176,177]. Kynurenine metabolites act on neuronal glutamate receptors and affect memory, anxiety-like and stress-like behaviours[175]. In fact, germ-free versus specific pathogen-free mice respond differentially in behavioural tests used to model depression-like phenotypes after depletion of dietary tryptophan (and, thus, all tryptophan microbial metabolites)[27].

Besides neurotransmitters, tyrosine can also be metabolized by the microbiota into other simple phenols such as 4-ethylphenol or *p*-cresol. These metabolites are rapidly sulfated by the host to 4-ethylphenyl sulfate (4EPS) or *p*-cresyl sulfate, respectively. 4EPS is elevated in a mouse model of ASD and schizophrenia, as well as in samples from children with ASD[178], and was shown to be sufficient to cause an anxiety-like phenotype when injected into wild-type mice[46]. *p*-Cresyl sulfate has been identified as a potential urinary biomarker for young children with ASD, and is correlated with altered oligodendrocyte markers in a mouse model of social and depressive-like behaviours, although these findings currently remain correlative[179,180].

Another amino acid affected by gut microorganisms is the major excitatory neurotransmitter glutamate, which is metabolized by a bacterial glutamate decarboxylase system to become the major inhibitory neurotransmitter GABA[13,181,182]. GABA can be further metabolized by bacteria to succinate by GABA aminotransferase and succinic semialdehyde dehydrogenase. Furthermore, metabolites either produced or influenced by the microbiota that affect the host GABA system have also been identified, such as γ-glutamyl amino acids, whose lowered levels are the mediators of diet-induced improvements in a mouse model of seizures[183]. GABA-producing bacteria have been shown to alleviate depression-like and anxiety-like behaviours in mouse models[51], and a strain engineered to produce GABA was sufficient to reduce sensitivity to visceral pain in rats[184]. A GABA-producing microbiota is negatively associated with depression in patients[185], and abnormalities in the glutamate/GABA circuits in the brain have been hypothesized as key in anxiety disorders, major depressive disorder, bipolar disorder, schizophrenia and ASD[186–189].

Arginine can be metabolized to four polyamines by the microbiota, which are present in all mammalian cells and play roles in many general processes of cell growth and differentiation, as well as regulating synaptic plasticity and memory formation via glutamate receptors[190]. These polyamines are generated sequentially from arginine to agmatine, then putrescine, followed by spermidine and, then, spermine[191,192]. Agmatine is a ligand for α_2-adrenergic and imidazoline receptors in the brain[193–196]. Dysregulation of the polyamine system has been implicated in mood disorders, depression and Alzheimer disease, and polyamines have been studied as preclinical therapeutics for depression and anxiety-like behaviours, cognitive decline and drug dependency[197–203]. As most mammalian neurotransmitters are derived from amino acid precursors, we speculate that bacterial transformation of amino acids into molecules that affect behaviour may represent a renewed microbial endocrinology focus in neuroscience[204] that is worthy of further study.

Complex plant polysaccharides. Dietary fibre, made of complex carbohydrate polysaccharides, is not digested by the host and reaches the colon, where it is fermented by intestinal microorganisms with a diverse class of glycoside hydrolases and polysaccharide lyases into millimolar levels of SCFAs[205,206]. SCFAs, mainly butyrate, propionate and acetate, are a rich energy source for colonic epithelial cells, and the remaining pool enters the systemic circulation where they may subsequently influence neurological function and development, seemingly for better or for worse, depending on the context. For instance, SCFAs were sufficient to exacerbate motor symptoms in a germ-free Parkinson disease mouse model[40], but they improved recovery from an experimental stroke mouse model[207]. Acetate has been shown to cross the BBB in mice and reduce feeding behaviours[208,209]. Propionate protects the BBB through signalling via the G protein-coupled receptor (GPCR) FFAR3 (REF.[210]) and improves multiple sclerosis symptoms in patients[211], but injections of propionate have also been used to induce a rodent model of ASD[212,213]. Butyrate is a potent inhibitor of histone deacetylases (HDACs), which regulate epigenetic signals of gene activation. As lowered histone acetylation is a characteristic of multiple neurodegenerative diseases[214], the pharmacological use of butyrate has been widely explored. Some preliminary success for butyrate treatment has been seen in beneficially lowered inflammation in mouse models of Huntington disease, Parkinson disease, ischaemic

Glossary

Bile acids
Complex lipid products of host cholesterol metabolism that play a major role in fat digestion and signalling in energy metabolism. Host bile acids (primary bile acids) are commonly modified by bacteria into secondary bile acids.

Enterochromaffin cells
Neuroendocrine cells in the gut lining that aid in gastrointestinal motility and produce 90% of the body's serotonin in response to persistent intestinal signals.

Germ-free mice
Mice reared in conditions completely absent of microbial exposure.

Gut microbiota
An intestinal community comprising bacteria and other microorganisms including viruses, fungi, protists and archaea that permanently or transiently inhabit the lower gastrointestinal tract, especially the small intestine and colon.

Microorganism-associated molecular patterns
(MAMPs). Well-conserved components of microbial cells that are acutely detected by the innate immune system of the host throughout the body, including the brain.

Polyphenols
A vast class of thousands of plant-derived molecules containing at least one phenol group that are generally poorly absorbed by the host until being transformed by the gut microbiota into bioavailable and bioactive metabolites.

Short-chain fatty acids
(SCFAs). Fatty acids with chains of fewer than six carbons that are the end product of bacterial fermentation of complex polysaccharides and serve as energy source and signalling molecule in the host.

Specific pathogen-free mice
Mice conventionally colonized with a complete gut microbiota.

Steroid hormones
Circulating signalling molecules derived from cholesterol with an organic chemical structure consisting of four carbon rings and various regulatory roles in the host.

Vagus nerve
A principle neuronal connection between the gut and brain, comprising a bundle of neurons that sends and receives signals directly between gut tissue (and other organs) and the brainstem. These signals can then be further transmitted throughout the brain.

stroke, Alzheimer disease and memory impairment[215–224].

Polyphenols. Polyphenols comprise a vast class of thousands of plant-derived molecules containing at least one phenol group, and are being extensively studied as therapeutics for neurological disease[225]. Most polyphenols are generally poorly absorbed until being transformed by the gut microbiota into bioavailable and bioactive metabolites[226,227]. Bacterial hydrolysis, acylation and/or esterification is followed by host modification by methylation, sulfation, hydroxylation or glucuronidation before these metabolites re-enter the gastrointestinal tract or reach other peripheral tissues[228,229]. Phenolic metabolite levels are known to be altered in the brain after oral administration of parent polyphenols[230–232]. Specific bacterial metabolites of oral polyphenol treatment that were measured in the brain, such as 3-hydroxybenzoic acid and 3-(3′-hydroxyphenyl)propionic acid, were shown to be capable of inhibiting hallmark amyloid aggregation and slowing progression of Alzheimer disease pathophysiology[233–235]. Polyphenols were also protective against stress-induced depression-like behaviours via decreased inflammation and modulated synaptic plasticity through metabolites such as quercetin-3-*O*-glucuronide and malvidin-3-*O*-glucoside[236]. One polyphenol, ferulic acid, is liberated into circulation by gut microorganisms harbouring the ferulic acid esterase gene[237]. Ferulic acid administration stimulates neurogenesis in a corticosterone-treated depression mouse model, and is protective in mouse models of Alzheimer disease and cerebral ischaemia[238–240]. Polyphenols in treatments such as grape seed extract and resveratrol show promise in treating neuropathology and cognitive defects in mouse models of Alzheimer disease, Parkinson disease and tauophathies[233,235,241–244], but further tests with pure polyphenols are needed. Recently, it was shown that plant-derived epigallocatechin gallate can prevent motor symptoms induced by specific gut bacteria in a model of Parkinson disease[245]. Some polyphenols are phytoestrogens, which are metabolized by gut bacteria into equol and enterolactone derivatives[246–249]. Phytoestrogen metabolites can be either agonistic or antagonistic to oestrogen receptors and may have an impact on the neuroprotective pathways activated by classic oestrogen receptor ligands, although this structural class is large and heterogeneous, and direct effects on the brain remain to be conclusively shown[250,251].

Fig. 3 | **Mechanistic examples of the routes of gut–brain communication.** There are several different ways in which gut microbial metabolites can influence brain function. Specific examples are shown of vagus nerve modulation, enterochromaffin cell modulation, direct brain exposure and immune-mediated communication. In the vagus nerve modulation panel, an example is shown where dietary tryptophan is converted to indole when mice are monocolonized by an *Escherichia coli* strain expressing the TnaA tryptophanase enzyme (TnaA + *E. coli*) compared with monocolonization with the control *E. coli* strain lacking TnaA, where no indole is produced. Bacterial modification of tryptophan was shown to result in activated vagal neurons and increased anxiety-like and depression-like behavioural phenotypes in the animals. In the enterochromaffin cell modulation panel, an example is shown where spore-forming bacteria from the Clostridiaceae and Turicibacteraceae families produce various metabolites including secondary bile acids, amino acid metabolites and short-chain fatty acids (SCFAs), which induce serotonin production by enterochromaffin cells and lead to elevated levels of circulating serotonin. We speculate that these serotonin levels may influence vagal nerve activity and/or brain levels of serotonin, denoted with a question mark in the figure. In the third panel, direct brain exposure via circulation, an example is shown where parent polyphenols, such as those found in grape seed extract, are modified by the microbiota into various phenolic metabolites that can be subsequently measured in the brain in association with reduced amyloid plaques and improved cognition. In the final panel (bottom right), immune system mediated, examples are shown where, on the left, a healthy diet including complex polysaccharides is fermented into SCFAs by the microbiota, which play important roles in G protein-coupled receptor (GPCR) signalling, histone deacetylase (HDAC) inhibition and lowered systemic inflammation that lead to decreased neuroinflammation. On the right, unbalanced microbiota can lead to altered levels of inflammatory bacterial lipopolysaccharide (LPS), which can lead to elevated neuroinflammation and depression-like behaviour via directly entering the brain or by inducing an elevated systemic immune response.

Other metabolites. Microbial GUS enzymes in the intestines remove glucuronide groups that mark metabolites for excretion by the host. As a result, the microbiota restores the original molecule and facilitates reuptake of the molecule back into the bloodstream[252,253]. This process has been shown to directly regulate levels of many of the exogenous and endogenous compounds described herein[168,254–256].

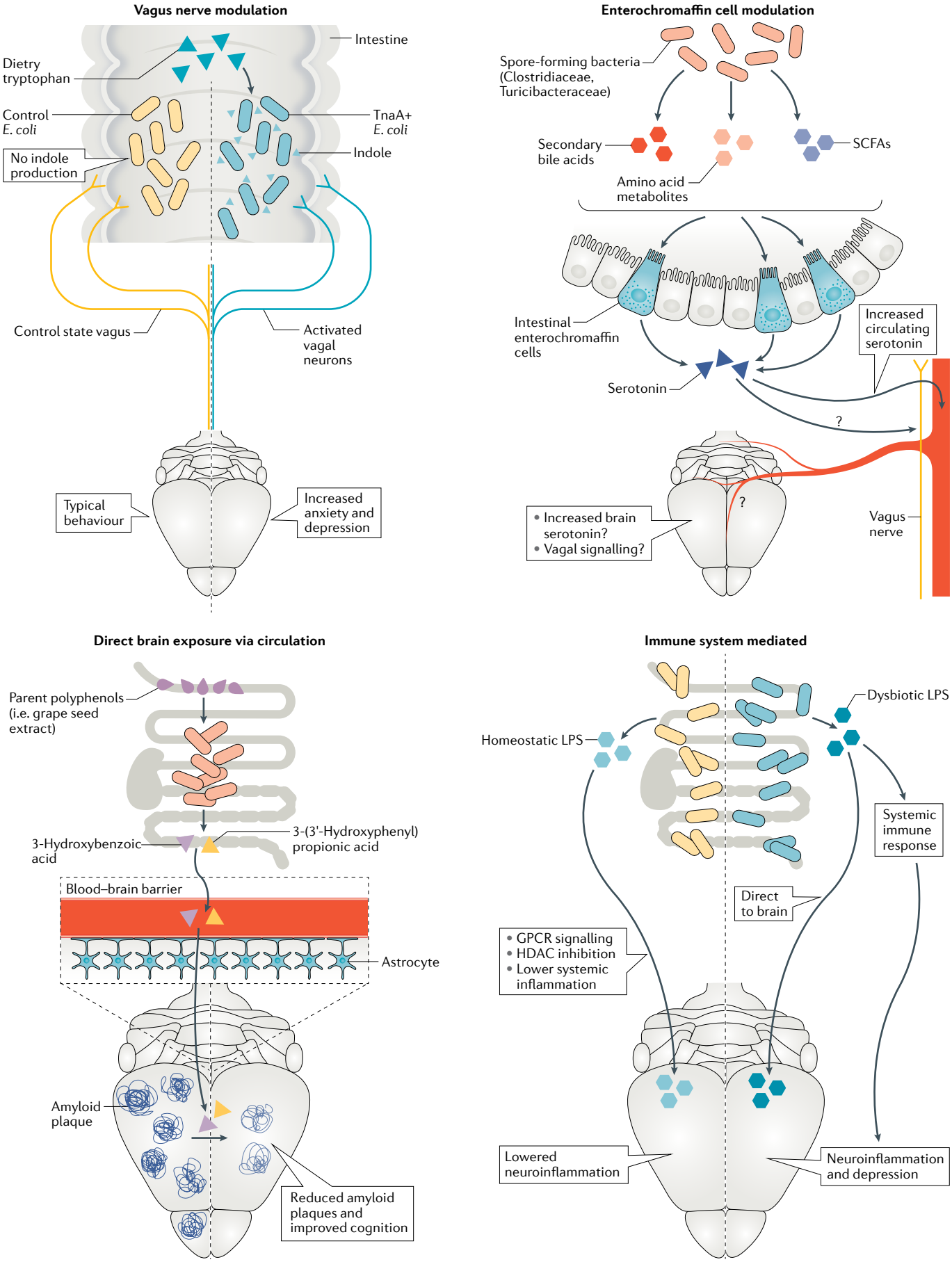
The gut microbiota also generates vitamins B and K[67,257–261], as well as unique lipid metabolites such as conjugated linoleic acids, hydroxy fatty acids and sphingolipids, several of which show biological activity in host health and disease and are known to be produced by particular bacterial species[123,125–128,262–265]. Owing to the need for vitamins B and K during brain development, the high lipid content of the brain and the importance of lipids in signalling pathways, future work may illuminate connections of microbial lipid and vitamin metabolites with brain function.

Research into the production and function of bacterial metabolites has established that active chemical messaging occurs from the gut to the brain. Other bacterial molecules could have as yet undefined neuroactive properties, including any of the thousands of recently identified (but still uncharacterized) short peptides from the gut microbiota[266]. Given that identifying and characterizing the small molecules and peptide repertoires produced by the microbiota is a relatively new endeavour, it is likely that further neuroactive microbial metabolites will continue to be discovered. Defining mechanisms of action may lead to various health applications.

Routes of microbiota–brain signalling

Conduits of communication from the gut microbiota to the brain include activation of the vagus nerve, stimulation of endocrine cells (including enterochromaffin cells), immune-mediated signalling and transport of gut-derived metabolites from the circulation into the brain. All routes comprising the gut–brain axis are thought to be co-opted by the microbiota to impact brain activity and behaviour, and signalling through any one of them may be intertwined with other routes (FIG. 3).

Vagus nerve activation. The vagus nerve directly links the muscular and mucosal layers along the gastrointestinal tract to the brainstem and is a well-established signalling pathway affecting feeding, anxiety-like, depressive-like and social behaviours[51,267,268]. Enteric pathogens and probiotics affect these behaviours through activation of vagal neurons, which then alters downstream neurological activity, including altered BDNF, GABA and oxytocin signalling in the brain[51,267–269]. These responses are ablated following vagotomy, which severs the vagus nerve, but the specific bacterial metabolites mediating these effects remain largely unidentified. One recent study did measure the effects of a specific metabolite through vagus signalling, although additional routes of signalling could also be involved[173]. In this work, rats were mono-colonized with either an *Escherichia coli* strain that converts


Vagus nerve modulation
Intestine
Dietry tryptophan
Control E. coli
TnaA+ E. coli
No indole production
Indole
Control state vagus
Activated vagal neurons
Typical behaviour
Increased anxiety and depression
Enterochromaffin cell modulation
Spore-forming bacteria (Clostridiaceae, Turicibacteraceae)
Secondary bile acids
SCFAs
Amino acid metabolites
Intestinal enterochromaffin cells
Increased circulating serotonin
Serotonin
?
• Increased brain serotonin?
• Vagal signalling?
Vagus nerve
Direct brain exposure via circulation
Parent polyphenols (i.e. grape seed extract)
3-Hydroxybenzoic acid
3-(3'-Hydroxyphenyl) propionic acid
Blood–brain barrier
Astrocyte
Amyloid plaque
Reduced amyloid plaques and improved cognition
Immune system mediated
Homeostatic LPS
Dysbiotic LPS
Systemic immune response
Direct to brain
• GPCR signalling
• HDAC inhibition
• Lower systemic inflammation
Lowered neuroinflammation
Neuroinflammation and depression

dietary tryptophan into indole with the *tnaA* tryptophanase or a mutant *E. coli* deficient in indole production. Rats exposed to indole in the gut displayed increased anxiety-like and depressive-like behaviours and activated vagal neurons[173].

Enterochromaffin cell stimulation. Enterochromaffin cells are endocrine cells in the gut lining that produce and secrete 90% of the body's serotonin in response to persistent intestinal signals[270]. Enterochromaffin cell production of serotonin impacts its circulating levels[130,167,271,272] and has the potential to influence brain activity directly or indirectly. Improved performance in mouse models of depression have been shown by probiotic treatment with *Bifidobacterium* spp. in a study that concurrently observed an increase in serotonin levels in the brain and also increased secretion of the serotonin precursor in enterochromaffin cells in vitro. However, no mechanistic connection between bacterial treatment, potential serotonin regulation and depressive-like phenotypes has been proved[273]. Colonic enterochromaffin cells do express receptors for, and respond to, various microbial metabolites, including MAMPs, SCFAs, aromatic amino acid metabolites and secondary bile acids[274–278]. One bacterial subset recently identified to greatly promote serotonin biosynthesis from enterochromaffin cells are spore-forming bacteria such as *Clostridia* spp. A collection of metabolites made by these bacteria in vivo were shown to be sufficient for serotonin-induction activity in vitro, including α-tocopherol, butyrate, cholate, deoxycholate, *p*-aminobenzoate, propionate and tyramine[130]. A subset was individually tested with temporal intestinal administration as well, and deoxycholate, α-tocopherol, *p*-aminobenzoate and tyramine were each sufficient to induce production of serotonin by enterochromaffin cells[130]. Interestingly, recent work showed that oral administration of a selective serotonin reuptake inhibitor, which increases bioavailability of gut serotonin and is used to treat depression, may be dependent on vagus nerve activation for its improvement of depressive-like behaviour in mice[279]. This supports the possibility that enterochromaffin cell production of serotonin has the potential to relay signals beyond the gut and reach the brain, possibly by intersecting with other known routes of gut–brain signalling in both developmental and acute contexts.

Immune-mediated signalling. The gut microbiota provides cues for the maturation of the neuroimmune system, and a loss of these cues during development results in lifelong dysfunction of this system[280]. However, chronic exposure to inflammation driven by shifts in gut microbiota and increased intestinal permeability may also factor into various neurological diseases[70]. Bacterial metabolites that serve as MAMPs, such as LPS, have been used to activate the immune system in models of ASD and schizophrenia, and also induce depression-like symptoms in mice[75,76,281]. Other gut metabolites likely dampen chronic inflammation. SCFAs, for example, interact closely with the immune system through activation of GPCRs and inhibition of HDAC activity. A high-fibre diet, leading to higher levels of SCFAs, results in lower levels of circulating pro-inflammatory cytokines[282,283]. Activation of GPCRs (FFA2 and GPR109a) by SCFAs can inhibit inflammatory signalling pathways, and HDAC inhibition by SCFAs, especially butyrate, leads to lowered inflammation in vivo[117,284–286]. These examples likely represent initial discoveries into the potential impacts of microbial molecules on neuroimmune signalling.

Direct transfer of metabolites to the brain. Many microbial metabolites produced in the gut can pass into systemic circulation at varying levels and rates. One example is the polyphenolic metabolite group, where recent studies have shown that parent polyphenols are virtually undetectable in the bloodstream or urine, but that bacterial metabolites produced from polyphenol precursors enter circulation at levels sufficient to exert biological effects[287,288]. In fact, the brain appears to be a major target for some polyphenolic microbial metabolites[289,290]. Although in vivo evidence remains lacking, in vitro cultures have shown that polyphenol metabolites are able to cross BBB model systems and exert protective effects on neuronal cultures, mostly through a decrease in inflammatory responses[291,292]. Furthermore, derivatives of oral polyphenolic treatment were measured in the blood and brain of rats and were found to decrease aggregation of neurotoxic aggregates and promote neuroplasticity[231,233,293].

Although gut–brain connections are well established, clear mechanistic details of the bacterial molecules working through each conduit are still limited. Understanding how the microbiome signals from the gut to the brain may provide insights into rational drug discovery platforms directed to targets in the gastrointestinal tract, which may overcome current challenges in the delivery of drugs to targets in the brain.

Cell-specific effects in the brain

Studies continue to build on the foundational understanding of the gut–brain axis to explore which cells in the brain are affected directly or indirectly by specific bacterial metabolites. Much work is needed to systematically demonstrate that these chemical messengers derived from gut bacteria influence the development or function of specific brain cells. Here, we summarize the current evidence that gut microbial metabolites may affect cells in the brain (FIG. 4).

Neurons. As the primary signalling cell of the brain controlling behaviour, neurons may, in essence, be the ultimate target affected by every metabolite described in this Perspective. All unidentified metabolites exerting the effects of bacterial communities that influence the vagus nerve probably activate neurons. More specifically, neurotoxins provide a stark example of bacterial molecules affecting neurons. Some neurotoxins are produced by commensal members of the microbiota and exert local or CNS effects to dysregulate or kill neurons[82,83,87–89]. The microbiota also produces or induces the production of neurotransmitters and their precursors, including serotonin, adrenaline, GABA, histamine, acetylcholine, glutamate and dopamine, which could dramatically affect the balance of excitatory and inhibitory neurotransmission in enteric, vagal, peripheral and central neurons[294]. Neurons also express pattern recognition receptors, and activation of these receptors has been shown to regulate neuronal differentiation, proliferation and axon generation as well as neuroinflammation. Some of this is likely due to host ligands, but MAMPs such as peptidoglycan are also detected in the brain and could be activating receptors such as TLR2, PGLYRP2 or NOD1, which are expressed in neurons, through similar mechanisms[71,295–297]. Neurons are also influenced by SCFAs, as acetate enters the brain and activates neurons in the hypothalamus[208,209]. Finally, in vitro screens identified neuroactive molecules produced by gut microorganisms, such as quorum sensing molecules, that affect the viability, morphology, differentiation and inflammatory responses of neurons[298]. Although the latter need to be validated

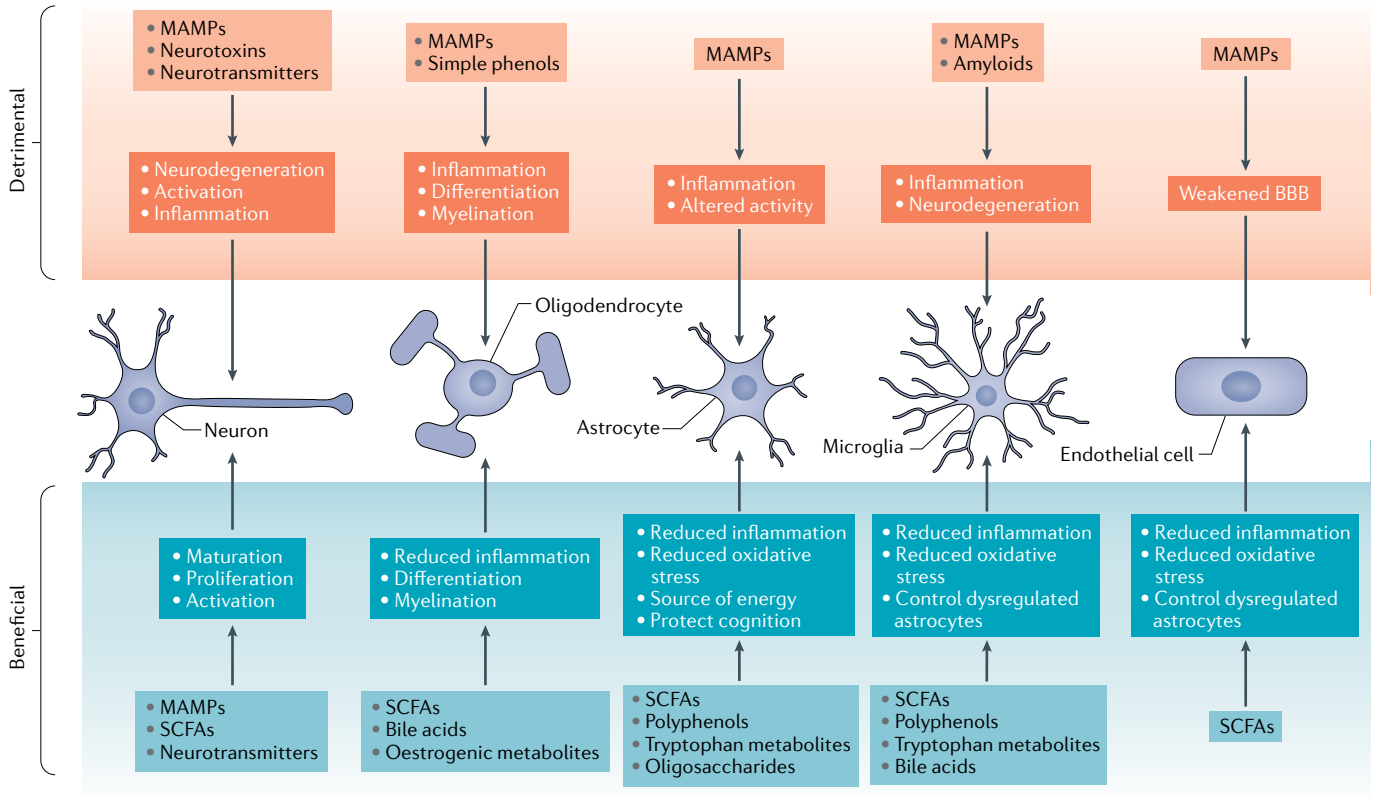


Fig. 4 | **Brain cell-specific effects of microbial metabolites.** Some microbial metabolites have known cellular targets in the brain. The beneficial and detrimental effects of these interactions are summarized. BBB, blood–brain barrier; MAMPs, microorganism-associated molecular patterns; SCFAs, short-chain fatty acids.

in vivo, they illustrate the possibility of a vast amount of interface between neurons and microbial metabolites.

Astrocytes. Astrocytes provide support to other cells and repair damage in the brain. Metabolites, including specific oligosaccharides and polyphenols, SCFAs and tryptophan metabolites, can affect astrocyte function. Tryptophan metabolites modulate the aryl hydrocarbon receptor in astrocytes and affect their activity by decreasing their inflammatory state and altering their interaction with microglia[299–302]. Polyphenolic metabolites and pure SCFAs such as butyrate have in vitro effects on astrocytes, and have been shown to decrease neuroinflammation and oxidation[303–305]. The SCFA acetate is used as an energy source by these cells in the brain[209]. Oligosaccharides and polyphenols such as those from the plant *Morinda officinalis*, which are metabolized by bacteria into SCFAs and other lipid derivatives, have been shown to have protective effects in Alzheimer disease through astrocyte function[306]. Astrocytes also express G protein-coupled bile acid receptor 1 (TGR5), which can be activated by bile acids with a resulting decrease in neuroinflammation, and may be relevant to hepatic encephalopathy[96].

Oligodendrocytes. Oligodendrocytes produce the myelin that insulates neuronal axons, with dynamic crosstalk between the two cell types even throughout adulthood. Metabolite effects on oligodendrocyte proliferation, differentiation and function could have widespread effects on neurological health. In the mouse model of the demyelinating disease multiple sclerosis, therapeutic gut microbiota manipulations have been successful and are accompanied by changes in metabolomic profiles associated with alleviated disease symptoms[50,307–312]. There is some evidence that improvements may be due to a decrease in inflammatory LPS levels, an increase in SCFAs and an altered profile of bile acids, although whether direct activity on oligodendrocytes occurs or whether they indirectly benefit from lowered inflammation has not been elucidated[129,308]. In vitro, the bacterial phenolic metabolite *p*-cresol may directly impair oligodendrocyte maturation and myelin production[180]. Another class of molecules known to affect oligodendrocyte differentiation and myelination are oestrogenic molecules[313–317]. Microorganisms do modify many oestrogenic metabolites[156], but a conclusive link between in vivo microbial production of these metabolites and oligodendrocytes has not yet been proved.

Endothelial cells. Blood vessels are lined with endothelial cells, which are the major cell type responsible for maintenance of the BBB that largely determines molecular entry into the brain[318]. Modulation of BBB permeability by microbial metabolites could greatly alter uptake of drugs, host molecules and other gut metabolites, but concrete examples of this mechanism remain elusive. For example, bacterial metabolites such as LPS from some bacterial species increase permeability in vivo in a dose and bacterial strain-dependent manner[319], and germ-free mice appear to have a leakier BBB than conventional mice[320]. LPS stimulation of endothelial cells can also lead to cerebral cavernous malformations, which in turn lead to seizures and strokes[321]. SCFAs have been shown to decrease permeability of the BBB through activating SCFA receptors expressed in endothelial cells and concurrent increases in expression of tight junction proteins that seal these cells into a successful barrier[210,320].

Microglia. The primary immune cells in the brain are known as microglia, and as such are responsible for much of the damage associated with neuroinflammation in diseases such as Parkinson disease and Alzheimer disease[322]. It is not surprising, then, that pro-inflammatory signals from MAMPs induce mature and cytokine-producing microglia whereas the generally anti-inflammatory cues from polyphenolic, SCFA and bile acid metabolites work via microglia to lower oxidative stress in the brain[286,323–325]. However, the effects of some of these signals on microglia are complex, as SCFAs, and probably other microbial signals, exacerbate symptoms in a germ-free mouse model of Parkinson disease[40]. Another recent work discovered that microbial tryptophan metabolites such as indoxyl-3-sulfate control the activation of microglia, which in turn alter the behaviour of astrocytes[300].

Although examples of cell-specific effects by the microbiome are both sparse and superficially described to date, these foundational studies represent critical steps in uncovering the underlying neuronal circuits, brain regions and systems-level connections of the gut microbiome–brain axis.

Perspectives

The gut microbiota, the gastrointestinal tract and the brain have historically been studied independently, but a growing appreciation for their interconnectedness may lead to transformative advances in biomedicine. Identifying and characterizing causal or contributing roles for particular microorganisms and microbial communities should be a primary focus of gut microbiome–brain research. However, the current state of the field remains largely correlative with descriptions of gut metabolite profiles in the context of neurologic states, whereas specific examples for effects by gut-derived molecules on brain cells, brain activity and behaviour are limited to a handful of studies. Additional progress is also needed to further understand the physical pathways employed by the microbiome in mediating communication between the gut and the brain. The various routes of direct and indirect chemical signalling are not mutually exclusive, and some metabolites potentially exert effects on multiple conduits to the brain.

As specific effects of microbial molecular messages and their gut–brain signalling routes continue to be uncovered, the potential increases for development of novel therapeutic principles and modalities. Continued, rigorous distinction between the correlative and causative links connecting gut metabolites to the brain may lead the way for new hypotheses for disease aetiology and treatment. For example, dietary interventions to shift the microbial community in favour of bacteria capable of producing beneficial chemical signals, or away from those generating pathogenic compounds, can be envisioned. Understanding of the microbial molecules crucial for health could allow the deployment of specific probiotics for specific maladies, based on empiric evidence that is lacking in current commercially available probiotic strains. Importantly, a deeper understanding of the mechanistic underpinnings for gut–brain connections in neurological diseases could lead to a world with targeted therapeutics directed at microbial effectors. Drugs could selectively inhibit production of harmful metabolites by targeting specific bacterial enzymes, which are evolutionarily divergent from human enzymes, thus increasing the available therapeutics while decreasing off-target effects. Further, microbial metabolites themselves may be therapeutically administered. The merger of microbiome and neuroscience research offers the possibility of understanding the basic 'wiring' and functions of the gut–brain axis, and also provides potential opportunities for near-term, actionable advances in human health.

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S.K.M. has financial interest in Axial Biotherapeutics. B.D.N. and R.K.-D. declare no competing interests.

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