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## Interactions between the microbiota, immune and nervous systems in health and disease

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### Abstract

The diverse collection of microorganisms that inhabit the gastrointestinal tract, collectively called the gut microbiota, profoundly influences many aspects of host physiology, including nutrient metabolism, resistance to infection and immune system development. Studies investigating the gut–brain axis demonstrate a critical role for the gut microbiota in orchestrating brain development and behavior, and the immune system is emerging as an important regulator of these interactions. Intestinal microbes modulate the maturation and function of tissue-resident immune cells in the CNS. Microbes also influence the activation of peripheral immune cells, which regulate responses to neuroinflammation, brain injury, autoimmunity and neurogenesis. Accordingly, both the gut microbiota and immune system are implicated in the etiopathogenesis or manifestation of neurodevelopmental, psychiatric and neurodegenerative diseases, such as autism spectrum disorder, depression and Alzheimer’s disease. In this review, we discuss the role of CNS-resident and peripheral immune pathways in microbiota–gut–brain communication during health and neurological disease.

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The human gastrointestinal tract is colonized by trillions of microorganisms collectively termed the gut microbiota. These intestinal microbes regulate many aspects of host physiology, including immune system maturation and function<sup>1–3</sup>. In addition, there is increasing evidence that the gut microbiota regulate brain development, function and behavior<sup>4–6</sup>. Although several immunological consequences of the microbiota are well documented<sup>1–3</sup>, immunomodulation by the microbiota is emerging as an important pathway that orchestrates microbiota–gut–brain communication<sup>7</sup>.

Far from an immune-privileged site, the brain harbors resident immune cells that defend against infection and injury, while also supporting neurons in remodeling circuit connectivity and plasticity. Molecules traditionally acknowledged for their functions in the peripheral immune system are now being recognized for their importance in neurodevelopment. For example, cytokines, typically regarded as immunomodulatory signaling factors, are present in the developing brain, where they regulate neuronal

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differentiation and axonal pathfinding<sup>8</sup>; complement proteins, which tag and kill microorganisms and damaged cells for immune clearance, target synapses for pruning during neurodevelopment<sup>9</sup>; and major histocompatibility complex (MHC) class I proteins, which enable antigen presentation by immune cells, modulate neurite outgrowth and synaptic plasticity<sup>10</sup>. Together, these findings contribute to the redefinition of immunomodulatory proteins as regulatory factors in normal brain development. Conversely, several factors traditionally acknowledged for their functions in the CNS are becoming recognized for their roles in the immune system. Various leukocyte subtypes produce and respond to classical neurotransmitters, which regulate depolarization or hyperpolarization of neurons<sup>11–14</sup>. Stimulation of dopaminergic neurons in the ventral tegmental area, for example, results in widespread activation of peripheral innate and adaptive immune cells<sup>15</sup>. Bidirectional communication between the nervous and immune systems is further facilitated by the recently defined brain lymphatic system, which connects peripheral lymphatic tissues to the CNS, and by the blood-brain barrier, which regulates endothelial passage of immune cells and associated factors<sup>16,17</sup>.

Microbial colonization of the intestine has a significant impact on neurophysiology and behavior<sup>4–6</sup>. Compared to conventionally colonized controls, germ-free (GF) mice, which are raised under sterile conditions, or mice depleted of their intestinal microbiota with oral broad-spectrum antibiotics exhibit substantial alterations in behaviors and neuropathologies that are relevant to neurodevelopmental, psychiatric and neurodegenerative disorders<sup>6</sup>. Given the immunomodulatory properties of the gut microbiota, immune cell pathways within and peripheral to the CNS have been implicated as important mechanisms mediating microbial modulation of brain function and behavior<sup>7,18</sup>. In this review, we discuss roles for the gut microbiota as an integral mediator of neuroimmune interactions. We examine how microbial influences on the activation of peripheral innate and adaptive immune cells regulate responses to neuroinflammation, brain injury, autoimmunity and neurogenesis. We further assess evidence that neuroimmune modulation by the microbiota can contribute to the etiopathogenesis or manifestation of symptoms relevant to neurobehavioral and neurodegenerative disorders, such as autism spectrum disorder, anxiety depression, Alzheimer's disease and Parkinson's disease. Finally, we highlight immunological, neuroendocrine and neuronal interactions that coordinate communication between the intestinal microbiota and brain.

## Development and function of brain resident immune cells

### Microglia

Microglia are the most abundant resident immune cells in the brain, comprising 5–20% of glial cells<sup>19</sup>. Derived from yolk sac erythromyeloid progenitors<sup>19,20</sup>, microglia perform canonical functions of myeloid cells, including phagocytosis, antigen presentation, cytokine production and activation of inflammatory responses<sup>19,21</sup>. Their extensive cellular processes enable rapid immune surveillance and clearance of debris and infectious agents, taking an estimated 2–5 h to survey the entire brain with limited physical migration<sup>21,22</sup>. Microglial activation states span a wide spectrum ranging from proinflammatory to tissue protective<sup>23–25</sup>. During neurodevelopment, microglia tag and clear synapses for pruning,

promote neuronal circuit wiring and produce cytokines and chemokines that guide neuronal differentiation<sup>19,24,26</sup>.

The microbiota influences microglial maturation and function (Fig. 1a). Compared to conventionally colonized controls, GF mice have increased numbers of immature microglia across gray and white matter of the cortex, corpus callosum, hippocampus, olfactory bulb and cerebellum<sup>27</sup>. Microglia in GF mice show longer processes and more branching, with elevated expression of colony stimulating factor 1 receptor (CSF1R), F4/80 and CD31, factors that decrease in expression with development toward an adult-stage phenotype<sup>27</sup>. Similar increases in immature microglia are observed after antibiotic treatment of conventional mice, though total microglia count remains unchanged<sup>27</sup>. This suggests differential effects of the microbiota on microglia, effects that depend on developmental timing and/or duration of microbial colonization. Consistent with this, gene expression differs between GF adult and newborn microglia when compared to their age-matched conventionally colonized controls<sup>20</sup>. Furthermore, several genes exhibit decreased expression in GF microglia, but more genes are downregulated in microglia from adult GF mice than in those from newborns<sup>20</sup>. The finding that microglia from newborn GF mice display altered gene expression profiles compared to those from newborn conventionally colonized mice suggests that the maternal microbiota may contribute to early life programming of microglial development.

Microglia from adult GF mice are also functionally impaired in response to challenge with lipopolysaccharide or lymphocytic choriomeningitis virus, displaying altered morphology and attenuated immune activation, including impaired induction of the proinflammatory cytokines interleukin (IL)-1 $\beta$ , IL-6 and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ )<sup>20,27</sup>. These functional deficits align with the finding that naive adult microglia from GF mice have decreased expression of several genes relevant to interferon responses, innate responses to stimulation, viral defense and effector processes<sup>20</sup>.

While the precise mechanisms by which gut microbes influence brain microglia remain unclear, there appears to be specificity of microglial modulation to particular bacterial taxa. GF mice that were colonized with a minimal community of three bacterial species—*Bacteroides distasonis*, *Lactobacillus salivarius* and ASF (altered Schaedler flora) 356, a member of *Clostridium* cluster XIV—maintained abnormalities in microglia<sup>27</sup>. This suggests that microbial effects on microglia are not regulated by bacterial load in general, but require greater diversity of the gut microbiota or are conferred by particular microbial species and functions not represented by the minimal community tested.

Notably, GF-associated alterations in microglial morphology, abundance and gene expression are normalized by postnatal supplementation with short chain fatty acids (SCFAs), primary products of bacterial fermentation<sup>27,28</sup>, suggesting that SCFA-producing bacterial species may restore abnormalities in microglia seen in GF or antibiotic-treated mice. However, ASF 356 is reported to produce the SCFAs propionate and acetate<sup>29</sup>, despite its failure to correct microglial abnormalities after colonization in the three-member community. This suggests a need to examine levels of SCFAs achieved by microbial colonization relative to dosages that were supplemented exogenously. Consistent with a role

for SCFAs in mediating effects of gut microbes on brain microglia, conventionally colonized mice harboring a deletion in G protein-coupled receptor 43 (GPR43), an SCFA receptor encoded by free fatty acid receptor 2 (*FFAR2*), exhibit abnormalities in microglia that are analogous to those seen in microbiota-depleted mice. As microglia do not express GPR43 directly<sup>27</sup>, whether the effects of the microbiota on microglia are mediated by direct signaling of SCFAs is unclear. Indeed, SCFAs are involved in a broad array of functions that influence gastrointestinal physiology, peripheral immunity, liver metabolism and blood-brain barrier integrity, which could indirectly contribute to effects on microglia. Future studies targeting specific bacterial taxa, particular SCFAs (acetate, propionate, butyrate) and conditional microglia-specific knockout of *FFAR2* are warranted.

Whether the microbiota affect microglial function during early postnatal development is not known but could have important implications for brain development and behavior later in life. During early postnatal life, microglia are integral for synaptic pruning, tagging synapses for clearance with complement proteins on the basis of neural activity<sup>30</sup>. Early exposure of conventional mice to antibiotics results in elevated cecal levels of SCFAs compared to those in controls<sup>31</sup>, raising the possibility that alterations in SCFAs could influence microglia during early postnatal development. Several neurological disorders, including autism spectrum disorder, Parkinson's disease, multiple sclerosis, anxiety, depression, stroke and amyotrophic lateral sclerosis, are all associated with both dysregulated microglia activity and dysbiosis of the gut microbiota (Table 1). Whether microbial effects on microglial maturation and function contribute to neurological symptoms are important questions for future study.

### Astrocytes

Astrocytes are the most abundant glial cells in the brain and exhibit a diverse array of functions, including the regulation of blood-brain barrier integrity, ion gradient balance, neurotransmitter turnover, cerebral blood flow and nutrient transport<sup>32,33</sup>. Astrocytes integrate information from adjacent glial, neuronal, vascular and immune cells to regulate neural excitability<sup>34</sup> and synapse formation<sup>35</sup>. Additionally, astrocytes are important for brain metabolism; as the main site of glycogen storage in the brain, astrocytes provide support when the brain is hypoglycemic<sup>33</sup>. Though they derive from neural progenitor cells and are not typically considered to be part of the CNS-resident immune system<sup>27</sup>, astrocytes perform immune-related functions, expressing pattern recognition receptors for detection of microbe-associated molecular patterns (MAMPs) and modulating neuroinflammatory responses through cytokine production and antigen presentation via MHC II<sup>36</sup>.

The gut microbiota modulates astrocyte activity via microbial metabolites that activate astrocyte aryl hydrocarbon receptors (AHR)<sup>37</sup> (Fig. 1b). Type I interferon signaling in astrocytes attenuates inflammation and symptoms of experimental autoimmune encephalomyelitis (EAE), a mouse model of multiple sclerosis. This effect is mediated in part by activation of AHRs. Gut microbes metabolize dietary tryptophan to produce natural AHR ligands, including indole-3-aldehyde and indole-3-propionic acid<sup>38,39</sup>. Consistent with this notion, depletion of the gut microbiota using the antibiotic ampicillin decreases levels of the AHR agonist indoxyl-3-sulfate (I3S) and worsens EAE disease scores<sup>37</sup>.

Supplementation of antibiotic-treated mice with the tryptophan metabolites I3S, indole-3-propionic acid and indole-3-aldehyde or with bacterial tryptophanases, which convert tryptophan to indole, improves EAE recovery. Similarly, peripheral administration of I3S or indole-3-aldehyde, or consumption of an indole-supplemented diet, improves EAE disease symptoms<sup>37</sup>. In human astrocytes, I3S treatment reduces expression of proinflammatory factors, including C-C motif chemokine ligand 2 (*CCL2*), tumor necrosis factor (*TNF*), nitric oxide synthase 2 (*NOS2*) and *IL6* (ref. 37). While much remains to be explored with regards to particular microbial taxa that regulate astrocyte function, the gut bacterium *Lactobacillus reuteri* is of interest because it is known to produce indole-3-aldehyde from dietary tryptophan<sup>37,38</sup>. Collectively, these findings suggest that microbial metabolites of dietary tryptophan can modulate the inflammatory status of astrocytes, with important consequences for neuroinflammation.

### Innate and adaptive immune cells in the CNS

Aside from glial subsets, innate and adaptive immune cells, including perivascular macrophages, CD4<sup>+</sup> T and CD8<sup>+</sup> T cells and mast cells, are also resident in the CNS<sup>21,26,40,41</sup>. While effects of the microbiota on these brain-resident immune cells have not been described, several studies revealed that the microbiota modulate peripheral myeloid cells, T cells and mast cells<sup>42</sup>, which share common hematopoietic progenitors with the brain subsets. For example, the microbiota are a major regulator of hematopoiesis and influence myeloid development in the embryonic yolk sac<sup>43</sup>, where microglial progenitors are believed to originate. Determining whether microbial effects on peripheral hematopoietic progenitors result in alterations in brain meningeal and/or tissue-resident immune cells would be important. Perivascular and choroid plexus macrophages would be of particular interest given their close localization to the vasculature<sup>21</sup> and potential exposure to circulating factors that are regulated by the microbiota.

### Peripheral immune cell responses and CNS interactions

#### CNS inflammation and injury

Intestinal bacteria are potent regulators of mucosal and systemic immune responses and contribute to the development of inflammatory disorders in the CNS (Fig. 2). In EAE, GF or antibiotic-treated mice exhibit reduced inflammation and disease scores compared to conventional mice<sup>44,45</sup>, suggesting a role for gut microbes in CNS inflammation. Studies investigating the contributions of specific members of the microbiota have revealed complex interactions between intestinal bacteria and CNS inflammation. Segmented filamentous bacteria are epithelial-associated bacteria that promote the development of IL-17A-producing T helper 17 (TH17) cells in the mouse small intestine<sup>46,47</sup>. Colonization of GF mice with these bacteria alone is sufficient to promote EAE compared to GF controls<sup>44</sup>, likely via induction of TH17<sup>48</sup>. Intestinal bacteria that promote immunoregulatory responses have been associated with protection against EAE. The human gut bacterium *Bacteroides fragilis* induces IL-10-producing regulatory T (T<sub>reg</sub>) cells in the mouse colon via capsular expression of polysaccharide A (PSA)<sup>49,50</sup>. While colonization of mice with wild-type *B. fragilis* reduces EAE severity, colonization with PSA-deficient *B. fragilis* restores EAE susceptibility<sup>45,51</sup>. Consistent with these findings, oral treatment of wild-type mice with

PSA protects against CNS demyelination and inflammation through a Toll-like receptor (TLR)-2-dependent pathway<sup>52,53</sup>. Metabolites produced by the gut microbiota have also been implicated in protection from EAE. Treatment of mice with SCFAs reduces EAE and axonal damage through increased T<sub>reg</sub> differentiation<sup>54</sup>. In myelin oligodendrocyte glycoprotein (MOG)-specific T cell receptor (TCR) transgenic 2D2 mice, intestinal microbes promote a subset of autoreactive intraepithelial lymphocytes. These MOG-specific CD4<sup>+</sup> lymphocytes are immunosuppressive and can protect wild-type mice from EAE in a lymphocyte activation gene (LAG)-3-dependent manner when adoptively transferred<sup>55</sup>. Altogether, gut bacteria influence the degree of CNS inflammation through modulation of pro- and anti-inflammatory mucosal and systemic immune responses. Despite these findings, whether antigen-specific responses or bystander activation of immune cells by the microbiota is involved in regulation of CNS inflammation requires further investigation.

Besides CNS inflammation, the microbiota also regulates the pathogenesis and resolution of CNS injury. In a mouse model of middle cerebral artery occlusion (MCAO)-induced ischemic brain injury, mice treated with the antibiotics amoxicillin and clavulanic acid show reduced infarct volume and improved sensorimotor function<sup>56</sup>. Neuroprotection is associated with reduced meningeal infiltration of small intestine IL-17<sup>+</sup>  $\gamma\delta$  T cells, suggesting that intestinal bacteria regulate lymphocyte trafficking to the brain and immune responses to brain injury. In contrast, pretreatment with the antibiotics ciprofloxacin and metronidazole reduces survival following MCAO<sup>57</sup>, suggesting that particular microbial species cause differential effects on brain injury recovery. Consistent with a causal role for the microbiota in brain injury, MCAO results in intestinal dysbiosis, and transfer of the MCAO microbiota to GF animals leads to increased proinflammatory cytokine production in the intestine and brain and increased infarct volumes<sup>58,59</sup>. In addition, transfer of fecal microbiota from naive animals to MCAO mice reduces brain lesions volumes in wild-type but not *Rag1*<sup>-/-</sup> animals<sup>58</sup>, suggesting a critical role for the adaptive immune system in protection from stroke. Bacterial translocation and altered microbiota composition have been observed in a mouse model of spinal cord injury<sup>60</sup>. Mice pretreated with antibiotics demonstrate delayed locomotor recovery, suggesting a protective role for intestinal microbes in this model. Furthermore, administration of the probiotic cocktail VSL3 reduces lesion size and improves locomotor recovery, which is associated with increased T<sub>reg</sub> cells in the mesenteric lymph nodes. IL-4-producing CD4<sup>+</sup> T cells in the CNS restore neuronal tissue homeostasis in this model<sup>61</sup>, suggesting a neuroprotective role for type 2 T helper (T<sub>H2</sub>) cells in CNS injury. However, the signals that promote tissue-protective T<sub>H2</sub> cells in the CNS may be independent of the intestinal microbiota and involve the release of damage-associated molecules<sup>62</sup>. Altogether, these findings suggest that modulation of the peripheral immune system by the microbiota plays a critical role in the development of and recovery from CNS injury.

### **The humoral immune system and CNS autoimmunity**

In addition to T cell-mediated mechanisms of CNS inflammation, B cells play an important role in the generation of CNS-reactive autoantibodies and the pathogenesis of neuroinflammatory disorders<sup>63,64</sup>. Intestinal microbes influence the development of behavioral disorders through modulation of humoral immune responses and antigen

mimicry. Streptococcal infection is often associated with the generation of CNS-reactive antibodies that lead to behavioral abnormalities collectively known as pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS). In the PANDAS animal model, where mice are immunized with group A  $\beta$ -hemolytic streptococci, mice develop behavioral abnormalities such as impaired motor coordination and repetitive rearing behavior<sup>65</sup>. Transfer of complete, but not IgG-depleted, sera from immunized mice is sufficient to induce behavioral deficits, suggesting that bacterial-infection-induced autoantibodies are critical to the development of PANDAS. Autoantibodies have also been implicated in the development of eating disorders, and intestinal bacteria appear to be involved in their generation. Antibodies produced in response to the heat shock protein ClpB derived from the bacterium *Escherichia coli* cross-react with  $\alpha$ -melanocyte-stimulating hormone ( $\alpha$ -MSH), a peptide critically involved in food intake<sup>66</sup>. Oral administration of wild-type but not ClpB-deficient *E. coli* results in the generation of ClpB- and  $\alpha$ -MSH-reactive antibodies and decreased food intake. These findings suggest a role for intestinal-bacteria-induced autoantibodies in behavioral disorders and provide the framework for future studies.

### Chronic inflammatory diseases

Chronic inflammatory diseases such as inflammatory bowel disease and chronic liver disease are commonly associated with impaired brain function and associated sickness behaviors<sup>67,68</sup>. Administration of probiotics can improve these symptoms by modulating peripheral immune pathways. In the bile duct ligation model of liver inflammation, mice routinely develop social disabilities, which were ameliorated following ingestion of the VSL3 probiotic cocktail<sup>69</sup>. Although probiotic treatment did not alter gut microbiota composition, it reduced the amount of circulating TNF- $\alpha$  and monocyte accumulation in the brain. Despite these findings, whether probiotics improve brain function by modulating peripheral immune responses requires further study.

### Neurogenesis

Intestinal bacteria have been demonstrated to regulate fetal and adult neurogenesis. Bacterial cell wall components cross the maternal–fetal interface and activate TLR2, which leads to fetal cortical neuroproliferation and impaired cognitive function during adulthood<sup>70</sup>. These data suggest that the maternal microbiota could influence offspring neurogenesis and subsequent behavioral changes. Studies assessing hippocampal neurogenesis in adult GF mice reveal increased proliferation relative to conventional mice<sup>71</sup>. However, colonization of GF mice after weaning does not reduce neuronal cell proliferation to conventional levels, suggesting a critical period in which intestinal bacteria regulate hippocampal neurogenesis. In contrast, antibiotic treatment decreases hippocampal neurogenesis and spatial and object recognition, which can be restored by exercise and probiotic VSL3 treatment<sup>72</sup>. Both exercise and probiotics are associated with CNS monocyte expansion. Depletion of monocytes reduces neurogenesis while adoptive transfer of monocytes to antibiotic-treated mice increases neurogenesis, identifying circulating monocytes as a cellular mediator of microbiota–gut–brain communication. More studies are necessary to precisely define mechanisms of microbial–immune interactions in the context of neurodevelopment.

## Associations with endophenotypes of neurological diseases

### Social communication and autism spectrum disorder

The gut microbiota influence the development of features related to behavioral disorders such as anxiety, depression and autism, and recent studies have begun to elucidate the cellular and molecular pathways involved<sup>4,5</sup>. In the maternal immune activation (MIA) animal model of autism spectrum disorder (ASD), in which administration of the TLR3 agonist poly(I:C) in pregnant dams results in offspring with behavioral phenotypes similar to those observed in autism, MIA offspring exhibit increased intestinal permeability and alterations in the composition of the gut microbiota<sup>73</sup>. Oral administration of the human gut bacterium *B. fragilis* to MIA offspring during weaning ameliorates microbiota dysbiosis and significantly restores behavioral abnormalities during the open field exploration, prepulse inhibition, marble-burying and ultrasonic vocalization tests. However, PSA-deficient *B. fragilis* and some other Bacteroides members are also able to protect MIA offspring, suggesting that alterations of these behaviors is not due to PSA-specific modulation of mucosal and systemic immune responses. Instead, it was proposed that *B. fragilis* treatment alters the composition of serum metabolites and reduces the anxiety-associated molecule 4-ethylphenylsulfate. Further support for a link between intestinal dysbiosis and these symptoms is provided by the finding that a maternal high fat diet (MHFD) results in changes to offspring microbiota and abnormal social behavior<sup>74</sup>. Transfer of the control but not MHFD diet microbiota from offspring to GF mice improves their social impairments, suggesting a causal relationship between intestinal dysbiosis and these behavioral readouts. It was proposed that behavioral abnormalities in MHFD offspring are due to reduced expression of the neuropeptide oxytocin in the hypothalamus and reduced activity of the dopaminergic reward system. Collectively, these data suggest that the gut microbiota affect symptoms relevant to neurodevelopmental disorders through modulation of the host metabolome and neuropeptide production.

The host immune system, which is dynamically regulated by the gut microbiota, is also critical in the development of behavioral phenotypes in MIA offspring. MIA leads to elevated systemic levels of the proinflammatory cytokines IL-6 and IL-17A<sup>75,76</sup>. Consistent with a role for immune dysregulation in the development of behavioral abnormalities in MIA offspring, irradiation of the MIA offspring followed by bone marrow reconstitution from non-MIA mice reduces repetitive and anxiety-like behavior<sup>76</sup>. Administration of IL-6 in offspring is sufficient to trigger prepulse and latent inhibition deficiencies, and blockade of IL-6 but not interferon- $\gamma$ , IL-1 $\alpha$  or TNF- $\alpha$  in pregnant dams reduces behavioral deficits induced by MIA<sup>77</sup>. More recently, IL-17A was implicated as a critical inflammatory mediator in MIA. MIA offspring from mice lacking T cell-derived IL-17A are protected from developing impairments in the ultrasonic vocalization, sociability and marble-burying assays<sup>75</sup>. Furthermore, intraventricular IL-17A administration in fetuses is sufficient to elicit abnormalities in these behavioral tests. Given the function of IL-6 in promoting differentiation of T<sub>H</sub>17 cells, these data suggest that IL-6 and IL-17A act in concert to promote MIA-induced behavioral abnormalities. Since IL-17A and T<sub>H</sub>17 cells are regulated by the gut microbiota, these findings also raise the possibility that MIA-induced immune



dysregulation is linked to intestinal dysbiosis. Further studies are required to address the contribution of intestinal bacteria in immune dysregulation and disease outcome in ASD.

### **Stress, anxiety and depression**

Major depressive disorder (MDD) is a mood disorder generally diagnosed when patients experience a depressed mood or a loss of interest or pleasure in daily activities for more than 2 weeks. The precise etiology of depression is not well understood but involves stress-induced changes in neural circuitry and neuroendocrine pathways<sup>78</sup>, activation of the immune system<sup>79</sup>, and interactions between the host and microbiota<sup>5</sup>. Mice lacking a normal gut flora display reduced basal and stress-induced behavioral impairments associated with anxiety and depression, and these phenotypes are restored following intestinal colonization<sup>80</sup>. In response to dextran sodium sulfate (DSS)-induced intestinal inflammation, mice exhibit increased latency to step down from an elevated platform, a behavioral test measuring anxiety, which is ameliorated by probiotic administration of *Bifidobacterium longum*<sup>81</sup>. Similarly, in the maternal separation model of depression, rats display increased immobility during the forced swim test and elevated proinflammatory cytokines, which are restored to normal levels following treatment with the probiotic *Bifidobacterium infantis*<sup>82</sup>. Intestinal colonization with particular *Lactobacillus* strains produces antidepressive effects during steady state or in response to stress<sup>83,84</sup>. One study showed that maternal-separation-induced behavioral impairments in the stepdown, light-preference and tail suspension tests require the presence of a complete gut microbiota, which suggests a causal relationship between intestinal bacteria and depression-related endophenotypes<sup>85</sup>. Furthermore, humans with MDD harbor a microbiota distinct from that of healthy controls, and fecal transfer of the MDD microbiota to GF mice enhances immobility time during the forced swim and tail suspension tests and reduces center distance traveled in the open field exploration test<sup>86</sup>. These findings are consistent with those of a separate study, which demonstrated reduced microbiota diversity in patients with MDD relative to healthy controls<sup>87</sup>. Antibiotic-treated rats receiving fecal transplants from humans with MDD exhibit behavioral impairments in the sucrose preference, elevated plus maze and open field exploration tests<sup>87</sup>. These results collectively support the hypothesis that intestinal bacteria influence responses to physical and psychological stress. While the cellular and molecular pathways that mediate microbiota–gut–brain interactions in stress-associated disorders appear to involve modulation of the immune system<sup>82,88</sup>, host metabolism<sup>86</sup> and/or vagal nerve stimulation<sup>81,84</sup>, detailed mechanisms are unclear. Given the immunomodulatory properties of intestinal bacteria and probiotics<sup>82,88</sup>, it is likely that alterations in immune homeostasis due to host–microbiota interactions can lead to changes in brain function through the hypothalamic–pituitary–adrenal (HPA) axis, a neuroendocrine, stress-sensing system that could be activated by proinflammatory cytokines<sup>89</sup>. Future studies using immunodeficient animals will be necessary to define the precise functions of the immune system in gut–brain communication in models of stress, anxiety and depression.

### **Neurodegeneration and aging**

Alzheimer's disease (AD) and Parkinson's disease (PD) are neurodegenerative disorders with complex etiologies including age, genetic and environmental components. In AD, deposition of protein aggregates composed of amyloid- $\beta$  peptide and tau in CNS tissues

impairs cognitive function. However, the host-intrinsic and extrinsic factors that regulate these processes are unclear. Accumulating evidence suggests that pathogenic microbes may contribute to neurodegeneration. Bacterial<sup>90,91</sup>, viral<sup>92,93</sup>, fungal<sup>94</sup> and parasitic<sup>95</sup> infections targeting the CNS are associated with increased risk of AD. These infections likely promote chronic inflammatory responses in the CNS of susceptible individuals that could contribute to hallmarks of neurodegeneration such as synaptic degeneration and amyloidosis<sup>96</sup>. Bacterial infection induces amyloid- $\beta$  peptide oligomerization, which has both antimicrobial and pathologic properties, proposing the idea that infection-induced amyloidosis may drive AD<sup>97</sup>. Aside from externally acquired microbes, one report demonstrated that mice representing a model of AD (APP<sup>PS1</sup>-Tg mice) derived under GF conditions exhibit reduced cerebral and serum amyloid- $\beta$  levels<sup>98</sup>. These results are consistent with reduced plaque deposition in male APP<sup>SWE</sup>/PS1<sup>E9</sup> mice, which also model AD, treated with broad-spectrum antibiotics<sup>99</sup>. In support of a role for intestinal microbes in promoting Alzheimer's disease, members of the host microbiota can regulate amyloidosis by producing their own amyloid peptides<sup>100</sup>. Additionally, manipulating the gut microbiota by antibiotic treatment or probiotic treatment alters learning and memory<sup>101,102</sup>. Despite these data, the role of microbiota-immune directed pathways in the development of AD requires further interrogation.

PD is a neurodegenerative motor disorder that is frequently associated with impaired gastric motility<sup>103</sup> and elevated levels of  $\alpha$ -synuclein in the intestine<sup>104</sup>, raising the possibility that the intestinal environment regulates the development of disease symptoms. One study revealed that the fecal microbiota of patients with PD had reduced abundance of Prevotellaceae compared to healthy controls while a subset of patients with severe postural instability and gait difficulty had elevated Enterobacteriaceae<sup>105</sup>, suggesting that these bacteria regulate motor function. Similar findings were reported in a separate study evaluating the gut microbiota in PD<sup>106</sup>. Patients also exhibit increased intestinal permeability and colonic inflammation<sup>107,108</sup>. Consistent with a potential role for microbes in promoting amyloidosis, the bacterial amyloid protein curli enhances  $\alpha$ -synuclein aggregation in rats and worms<sup>109</sup>. Altogether, these data warrant further studies exploring the contributions of the gut microbiota-immune axis to the development of PD.

## Neuroimmune pathways for microbial communication with the CNS

### Bacteria-derived and host-derived products

Alterations in intestinal bacteria composition and signaling events in the gut can influence brain function and behavior through several mechanisms (Fig. 3). Activation of innate immune responses following exposure to microbial factors requires the recognition of MAMPs via pattern recognition receptors. The most well characterized family of pattern recognition receptors is TLRs, which are expressed not only on innate immune cells but also CNS-resident cell populations, including neurons and glial cells<sup>110</sup>. Since TLR ligands derived from the intestinal microbiota can be found systemically during chronic inflammatory disorders<sup>111</sup>, these products may be able to directly trigger innate immune pathways to affect CNS function. Although systemic lipopolysaccharide administration drives CNS inflammation by activating TLR4-expressing brain-resident cells<sup>112,113</sup>,

experimental support for microbiota-derived MAMPs that trigger CNS inflammation is limited. However, one study demonstrated that peptidoglycan (PGN)-sensing molecules are highly expressed in the developing striatum and are reduced in expression in GF and antibiotic-treated neonates<sup>114</sup>. Mice deficient in PGN recognition protein 2 display increased sociability in the three-chamber social approach test, suggesting a role for PGN recognition in the CNS in social behavior.

Intestinal bacterial colonization modulates the host metabolome, which influences CNS function<sup>27,37</sup>. Circulating metabolites can enter the CNS and directly affect neuroactivity<sup>37</sup>. Conversely, particular metabolites can regulate the function of peripheral immune cells<sup>3,115</sup>, which then can influence brain function, potentially through the recently described brain lymphatic network<sup>116</sup>. How immune cells coordinate gut–brain communication and whether microbe-derived metabolites can directly modulate CNS function are areas of intense investigation.

Neurotransmitters are of particular interest in light of studies demonstrating that the gut microbiota can modulate its production<sup>117,118</sup> and that particular gut microbes can synthesize neurotransmitters *de novo*<sup>119</sup>. The majority of the host's serotonin is derived from the gastrointestinal tract<sup>120</sup>, suggesting a role for the intestinal environment in modulating its synthesis. Consistent with this idea, GF mice have reduced levels of serum and colon serotonin compared to conventional controls<sup>39</sup>. Spore-forming bacteria in particular activate intestinal enterochromaffin cells to produce serotonin<sup>118</sup>. Furthermore, metabolites upregulated by spore-forming bacteria colonization as well as SCFAs can directly promote the production of serotonin and expression of the serotonin biosynthetic enzyme *Tph1* in enterochromaffin cells<sup>117,118</sup>. Microbiota-dependent regulation of neurotransmitter pathways has also been observed for GABA<sup>84</sup>, norepinephrine<sup>121</sup>, dopamine<sup>121</sup> and tryptamine<sup>122</sup>. Immune cells of both myeloid and lymphoid lineages express a wide range of neurotransmitter receptors and can respond to neurotransmitter stimulation by altering their inflammatory functions<sup>12</sup>. While these studies have direct implications for neurogastrointestinal health, future studies should also investigate the role of these microbe-mediated pathways in brain development, function and behavior.

### Neuronal signaling

In addition to modulating intestinal production of neurochemicals, gut microbes can communicate with the CNS via stimulation of the vagus nerve, a bundle of parasympathetic motor and sensory fibers that conveys information from peripheral organs such as the gastrointestinal tract to the CNS. Treatment of wild-type mice with the bacterium *Lactobacillus rhamnosus* increases center exploration in the open field test and decreases immobility time in the forced swim test, and this effect is abolished following vagotomy<sup>84</sup>. Increased latency in the step-down test of anxiety induced by DSS colitis also depends on the vagus nerve<sup>81</sup>. Further, treatment with *B. longum* during DSS colitis does not ameliorate impairments in the step-down test in vagotomized mice, identifying a critical role for afferent vagal stimulation in bacteria-mediated changes in behavior. Conversely, the CNS transmits signals to the intestine through the efferent fibers of the vagal nerve. These neurons control intestinal motility, release of neurochemicals and the intestinal immune

environment. Specifically, vagal nerve stimulation has been suggested to attenuate inflammatory responses through the neurotransmitter acetylcholine<sup>123</sup>, raising the possibility that the immunomodulatory properties of probiotic strains such as *Lactobacillus* and *Bifidobacterium* may depend on the vagus nerve. However, protection from DSS colitis conferred by *L. rhamnosus* and *B. infantis* was observed in both control and vagotomized mice<sup>124</sup>, suggesting that gut–brain communication via this pathway may be specific to certain bacterial strains and the inflammatory context. In addition to parasympathetic regulation, the sympathetic branch of the autonomic nervous system is also involved in intestinal homeostasis and modulates the intestinal immune environment<sup>59</sup>. Despite these findings, how intestinal microbes, sensory neurons and immune regulation are linked requires further study.

### Neuroendocrine pathways

Biochemical changes in the brain can also lead to changes in intestinal physiology. One of the main pathways by which this occurs is the HPA axis. In response to physical or psychological stress, hormones released from the hypothalamus, pituitary and adrenal glands collectively influence multiple organ systems to allow the host to adapt to the environment. For example, activation of the stress response through the HPA axis can lead to changes in intestinal permeability<sup>125–128</sup>, motility<sup>129,130</sup> and mucus production<sup>131,132</sup>. These events contribute to alterations in microbiota composition as demonstrated in mouse models of early-life and chronic stress<sup>85,133</sup>. Consistent with these findings, activation of the HPA axis affects immune cell responses. Glucocorticoids released by the HPA axis have profound anti-inflammatory influences on innate and adaptive immune cells but can also stimulate proinflammatory responses under certain conditions<sup>89,134</sup>. Stress-induced behavioral abnormalities may occur in a microbiota-dependent manner. Although maternal separation results in elevated serum corticosterone levels and increased acetylcholine release by the colon in both GF and conventional mice, it triggers behavioral alterations only in conventional mice<sup>85</sup>. Altogether, these findings support the idea that microbiota–gut–brain communication not only involves microbial modulation of brain function but also the reverse: CNS-induced biochemical changes result in altered intestinal biology, bacterial composition and immune function.

### Concluding remarks

Accumulating evidence indicates that brain-resident and peripheral immune cells are critically involved in orchestrating microbiota–gut–brain communication. The gut microbiota regulate the development and function of microglia and astrocytes, which mediate neurophysiological processes including neural development, neurotransmission, CNS immune activation and blood-brain barrier integrity. The microbiota also modulate peripheral immune responses, with important consequences for brain inflammation, injury and behavior. Microbial influences on innate and adaptive immune activation in the intestine, fetal–maternal interface and systemic circulation are associated with symptoms of various neuroinflammatory, neurodegenerative and psychiatric disorders. Collectively, these findings establish the CNS and peripheral immune systems as important cellular mediators of communication across the microbiota–gut–brain axis. However, molecular mechanisms

for how host–microbe interactions in the intestine remotely alter brain physiology remain largely unclear. Future investigations are necessary to define specific microbe-derived factors, immune effector functions and microbiota–immune pathways for modulating brain function and behavior. These studies will reveal fundamental biological insights for brain health, with the potential to inform the development of new microbial and immune-based therapeutic strategies for the treatment of neurological diseases.

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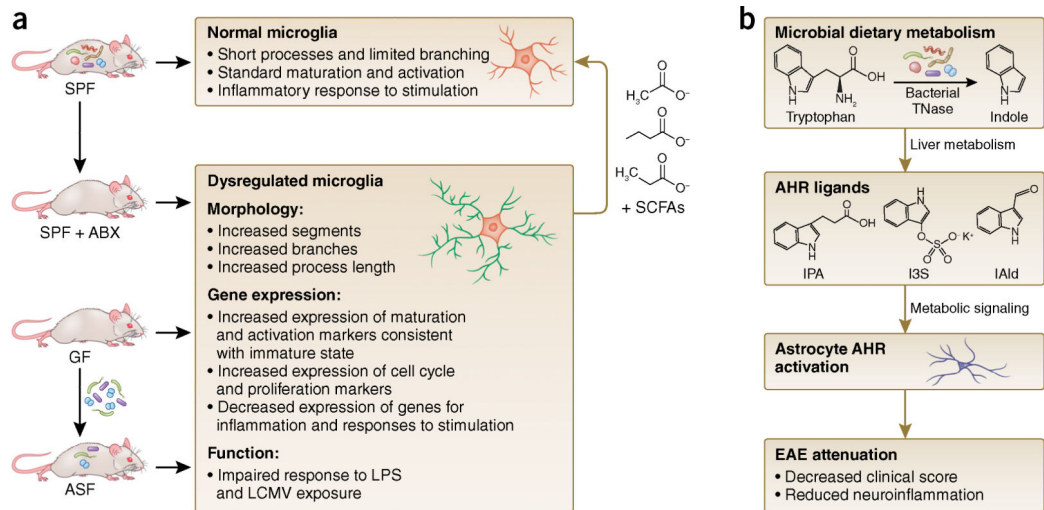


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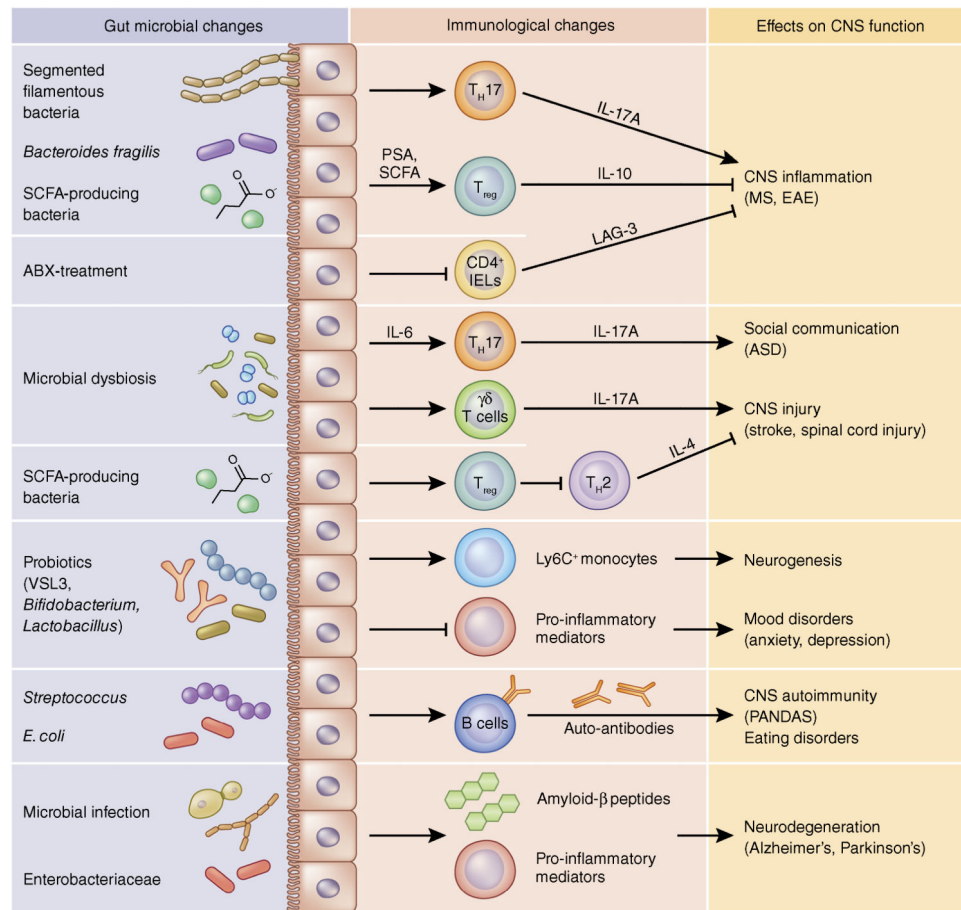
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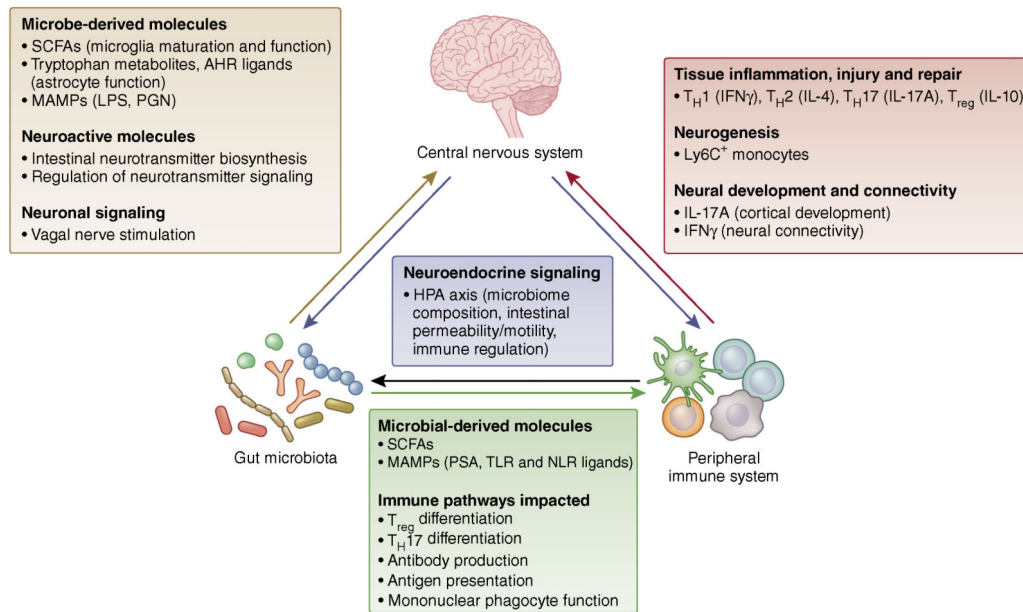
**Figure 1.**

Effects of the microbiota on microglia and astrocyte biology. **(a)** Microglial maturation and function are affected by the presence or absence of a complex microbiota. Compared to conventionally colonized (specific pathogen-free, SPF) controls, mice reared in the absence of microbial colonization (germ free, GF) have microglia with abnormal morphology, altered gene expression and impaired functional response to stimulation. Similar microglial abnormalities are seen in microbiota-depleted mice, produced by antibiotic treatment of SPF mice (ABX) or colonization of GF mice with three bacterial taxa from a limited altered Schaedler flora (ASF) consortium (*B. distasonis*, *L. salivarius*, and *Clostridium* cluster XIV). Microglial abnormalities in GF mice are corrected by supplementation with short-chain fatty acids (SCFAs), products of bacterial fermentation. **(b)** Microbial metabolites bind to the aryl hydrocarbon receptor (AHR) in astrocytes, reducing symptoms of EAE. Type I interferon signaling in astrocytes diminishes inflammation and decreases EAE clinical scores, and this effect is reversed by antibiotic treatment. Particular tryptophan metabolites produced by the microbiota stimulate AHR and reduce EAE clinical scores. This suggests that the microbiota have a direct effect on AHR signaling and inflammation in astrocytes, which may have relevance to multiple sclerosis, where patients show decreased tryptophan-derived metabolites in sera. TNase, tryptophanase; IPA, indole-3-propionic acid; IAld, indole-3-aldehyde; I3S, indoxyl-3-sulfate.



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**Figure 2.** Effects of the microbiota on peripheral immune cells and CNS function. Intestinal microbes in the gastrointestinal tract regulate peripheral immune responses, CNS function and behavior. Intestinal colonization by specific members of the microbiota is associated with activation of pro- or anti-inflammatory  $CD4^+$  T cell responses that regulate susceptibility to EAE. The material immune activation (MIA) model of ASD leads to microbial dysbiosis that is associated with elevated  $T_H17$  cell responses, which are sufficient to trigger social and behavioral defects. Mouse models of CNS injury (stroke, spinal cord injury) also appear to be regulated by microbiota-immune interactions. Oral administration of probiotics can elicit a population of Ly6C<sup>+</sup> monocytes that increase hippocampal neurogenesis and enhance memory responses. Probiotics such as *Bifidobacterium* and *Lactobacillus* have potent anti-inflammatory properties that reduce behaviors associated with anxiety and depression. Furthermore, microbial infections can trigger antibody-dependent CNS autoimmunity and promote neurodegeneration. Collectively, regulation of peripheral immune responses is a critical pathway by which the intestinal microbiota and exogenous microbial challenges influence CNS function and behavior. ABX, antibiotic treatment of SPF mice; IELs, intraepithelial lymphocytes; LAG-3, lymphocyte activation gene-3.



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**Figure 3.**

Crosstalk between the microbiota, immune system and CNS. Interactions between the intestinal microbiota, peripheral immune system and CNS are essential for the maintenance of host health. Recognition of microbial derived products such as microbe-associated molecular patterns (MAMPs) and metabolic by-products of microbes (short chain fatty acids, SCFAs) activates distinct immune pathways throughout the host. The microbiota and immune system can independently or cooperatively regulate neurophysiology. Therefore, a prevailing theme in studies aimed at understanding the microbiota–gut–brain axis involves the role of intestinal microbes in modulating CNS function through CNS-resident and peripheral immune pathways. Biochemical changes in the CNS can also lead to altered microbial composition and immune cell responses through the HPA axis. Altogether, these findings suggest that the microbiota, immune system and CNS communicate bidirectionally. Future studies investigating the functional outcomes of these bidirectional interactions will inform the development of new therapeutic strategies for the treatment of neurological disorders. IFN $\gamma$ , interferon gamma; LPS, lipopolysaccharide; NLR, Nod-like receptor; PGN, peptidoglycan; TLR, Toll-like receptor.

Table 1

Reported alterations in the gut microbiota in neurological and psychiatric disorders

Pathology type	Condition	Associated microbiota changes	Refs.
Autoimmune disease	Multiple sclerosis	Increased: <i>Methanobrevibacter</i> , <i>Akkermansia</i>	135
		Decreased: <i>Butyrivibrio</i>	
		Increased: Desulfovibrionaceae	136
		Decreased: Lachnospiraceae, Ruminococcaceae	
		Increased: <i>Pseudomonas</i> , <i>Mycoplana</i> , <i>Haemophilus</i> , <i>Blautia</i> , <i>Dorea</i>	137
		Decreased: <i>Parabacteroides</i> , <i>Adlercreutzia</i> , <i>Prevotella</i>	
		Increased: <i>Streptococcus</i> , <i>Eggerthella</i>	138
		Decreased: Clostridia clusters XIVa and IV, Bacteroidetes, <i>Faecalibacterium</i>	
		Increased: <i>Ruminococcus</i>	139
		Decreased: Bacteroidaceae, <i>Faecalibacterium</i>	
		Increased: <i>Blautia</i> , <i>Coproccoccus</i> , <i>Roseburia</i> , Proteobacteria	140
		Decreased: <i>Faecalibacterium</i> , Prevotellaceae	
Neurodegenerative disorders	Parkinson's disease	Decreased: Prevotellaceae	105
		Enterobacteriaceae correlate with motor impairments	
		Association with bacterial and viral infection	141
		SCI with upper motor neuron bowel syndrome: decreased <i>Pseudobutyrvibrio</i> , <i>Dialister</i> , <i>Megamonas</i>	142
Injury	Alzheimer's disease	SCI with lower motor neuron bowel syndrome: decreased <i>Roseburia</i> , <i>Pseudobutyrvibrio</i> , <i>Megamonas</i>	143
		SCI with neuropathic bladder: increased <i>Klebsiella</i> , <i>Escherichia</i> , <i>Enterococcus</i>	
		SCI with neuropathic bladder: decreased <i>Lactobacillus</i> , <i>Corynebacterium</i> , <i>Staphylococcus</i> , <i>Streptococcus</i> , <i>Prevotella</i> , <i>Veillonella</i>	
		Decreased: <i>Bifidobacterium</i> , <i>Lactobacillus</i>	144
Neuropsychiatric conditions	Major depressive disorder	Increased: Actinomycineae, Coriobacterineae, Lactobacillaceae, Streptococcaceae, Clostridiales, Eubacteriaceae, Lachnospiraceae, Ruminococcaceae, Erysipelotrichaceae	86
		Decreased: Bacteroidaceae, Rikenellaceae, Lachnospiraceae, Acidaminococcaceae, Veillonellaceae, Sutterellaceae	
		Increased: Enterobacteriaceae, <i>Alistipes</i> , Acidaminococcaceae, Fusobacteriaceae, Porphyromonadaceae, Rikenellaceae	145
		Decreased: Bacteroidaceae, Erysipelotrichaceae, Lachnospiraceae, Prevotellaceae, Ruminococcaceae and Veillonellaceae <i>Faecalibacterium</i> negatively correlated with depressive symptoms	
	Anxiety disorder	Probiotic administration of <i>B. longum</i> and <i>Lactobacillus helveticus</i> decreased anxiety	146



Pathology type	Condition	Associated microbiota changes	Refs.
Autism		Probiotic administration of <i>Lactobacillus casei</i> , <i>Lactobacillus acidophilus</i> , <i>L. rhamnosus</i> , <i>Lactobacillus bulgaricus</i> , <i>Bifidobacterium breve</i> , <i>B. longum</i> , <i>Streptococcus thermophilus</i> and <i>Bifidobacterium lactis</i> decreased anxiety	147
		Increased: <i>Lactobacillus</i> , <i>Desulfovibrio</i> , <i>Clostridium</i> , cluster 1	148
		Decreased: <i>Bacteroides/Firmicutes</i> , ratio	
		Increased: <i>Sutterella</i>	149
		Increased: <i>Clostridium</i> , <i>Bacteroides</i> , <i>Porphyromonas</i> , <i>Prevotella</i> , <i>Pseudomonas</i> , <i>Aeromonas</i> , <i>Enterobacteriaceae</i>	150
		Decreased: <i>Enterococcus</i> , <i>Lactobacillus</i> , <i>Streptococcus</i> , <i>Lactococcus</i> , <i>Staphylococcus</i> , <i>Bifidobacteria</i>	
		Increased: <i>Lactobacillus</i>	151
		Decreased: <i>Prevotella</i> , <i>Coprococcus</i> , <i>Veillonellaceae</i>	
		Increased: <i>Sutterella</i> , <i>Lachnospiraceae</i> , <i>Ruminococcaceae</i>	152
		Increased: <i>Lactobacillus</i>	153
		Decreased: <i>Bifidobacterium</i> , <i>Enterococcus</i>	
		Increased: <i>Bacteroidetes</i> , <i>Proteobacterium</i>	154
		Decreased: <i>Actinobacterium</i> , <i>Bifidobacterium</i>	
		Increased: <i>Clostridium</i> clusters I and II	155