

# Microbiome–Gut–Brain Axis: Implications for the Links Between Inflammatory Bowel Disease and Neuropsychiatric Disorders

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**Abstract:** The brain and gastrointestinal tract are closely interconnected as important sensory organs processing signals from both environmental and internal cues. Recent studies have shown that dysregulation of the gut microbiota in inflammatory bowel disease activates the gut immune system. The cross-talk mechanism along the gut-brain axis is implicated in the development of neuropsychiatric disorders such as autism, depression, anxiety, Alzheimer's disease, and Parkinson's disease. Here, we discuss the molecular mechanisms involved in signaling across the gut-brain axis, including the immune and neuroendocrine system, intestinal permeability, microbial composition, and bacterial extracellular vesicles. We focus on the link between specific inflammatory bowel disease, microbial genera and psychiatric and neurological disorders, and propose that the results of preclinical and clinical studies open up the possibility of targeting the gut microbiota to treat neuropsychiatric disorders that are altered by gut interactions.

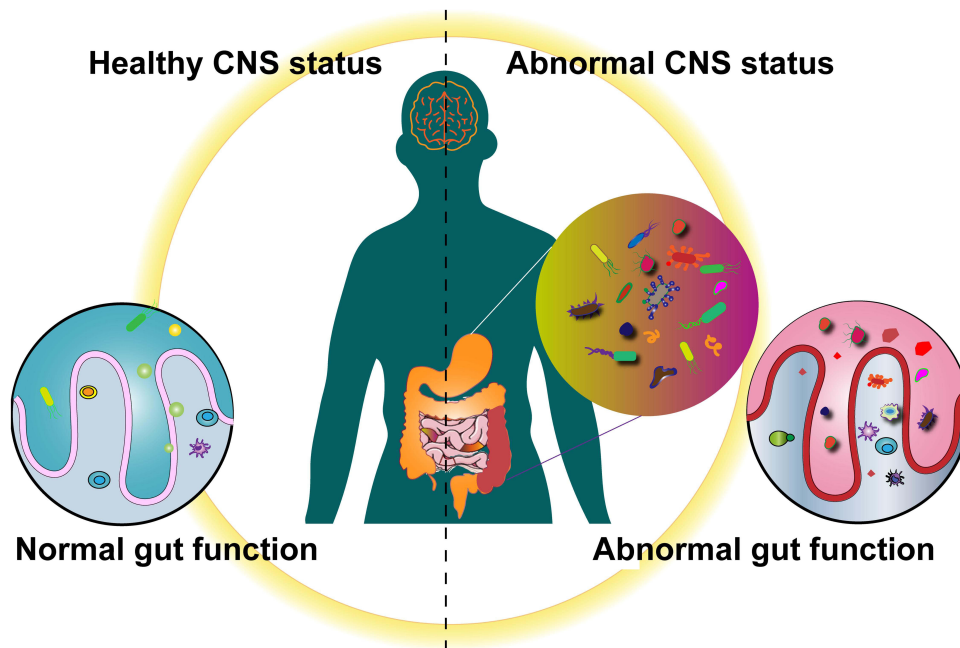
**Plain Language Summary:** There is a strong bidirectional communication between the brain and the digestive system. Dysregulation of the gut microbiota (GM) in inflammatory bowel disease (IBD) activates the gut immune system and contributes to brain disorders. Targeting the gut-brain axis has the potential to treat both neurological disorders such as depression, autism, Alzheimer's disease, and Parkinson's syndrome, and to ameliorate intestinal disorders such as IBD.

**Keywords:** Gut–brain axis, GBA, microbiome–gut–brain axis, MGBA, inflammatory bowel disease, IBD, neuropsychiatric disorders, probiotics, psychobiotics

## Introduction

The gut has certain self-regulatory functions. However, the gut is regulated by multiple systems such as neural, immune, and endocrine systems.<sup>1</sup> In addition, the gut is influenced by a complex intestinal environment constructed by the gut

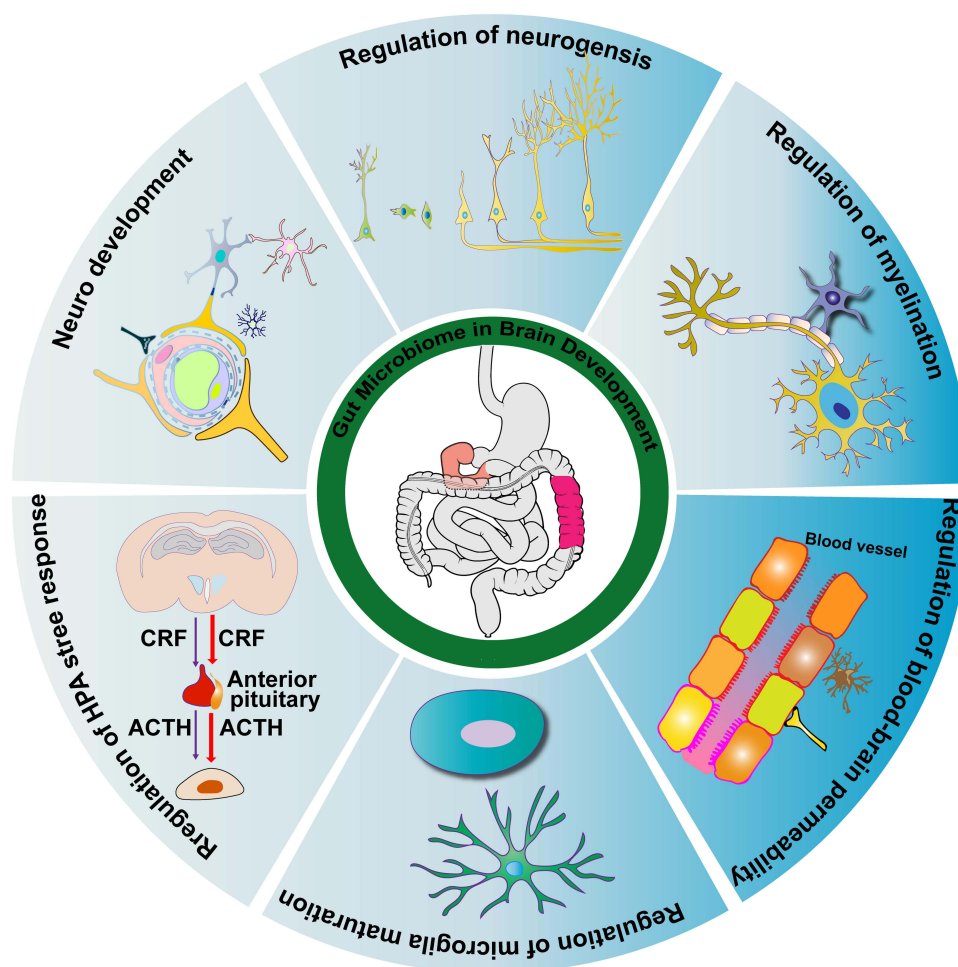
## Graphical Abstract



microbiota (GM), chemicals and physical conditions, in which GM serves the most important extrinsic factor.<sup>1</sup> Studies have shown that disorders of the GM are involved in the pathogenesis and development of inflammatory bowel disease (IBD), and interventions in disorders of the GM have become an important tool in the treatment of IBD.<sup>2</sup>

The brain is a regulatory organ, the high-level center of the nervous system. Through the nervous system, the brain regulates the functional activity of almost all organs of the body.<sup>3</sup> The brain is also a functional organ capable of generating consciousness through mental-psychological and behavioral activities.<sup>3</sup> At the same time, changes in gut function and alterations in the GM transmit information to the brain through multiple pathways, affect the regulatory and higher functions of the brain.<sup>4</sup> It has been found that IBD is often accompanied by neuropsychiatric symptoms, increasing the prevalence of each other, and there is a reciprocal facilitation effect in treatment.<sup>2</sup> There is also a strong link between disturbances in the GM and brain dysfunction. There is growing evidence of a gut-brain associated with aspects of their own or their children's neurodevelopment, neuropsychiatric disorders and the incidence of neurodegenerative diseases (Figure 1).<sup>4</sup>

This review discusses the influence of the GM in the occurrence and development of IBD, and focuses on the involvement of GM in the occurrence and development of neuropsychiatric disorders, such as depression, anxiety disorders, autism spectrum disorder (ASD), schizophrenia (SCZ), Alzheimer's disease (AD), and Parkinson's disease (PD). In addition to discuss the comorbidity of IBD and mental health disorders, this review explores the potential therapeutic value of the GM for IBD and neuropsychiatric disorders by summarizing the effects of the GM on the gut and brain. We searched for disease-specific diagnostic markers based on structural and omics changes in GM. Using GM as a therapeutic target, we study the effects of diet or medication on GM, and explore the therapeutic effects of GM interventions such as gut microecological regulators and GM transplantation on IBD or neuropsychiatric disorders.

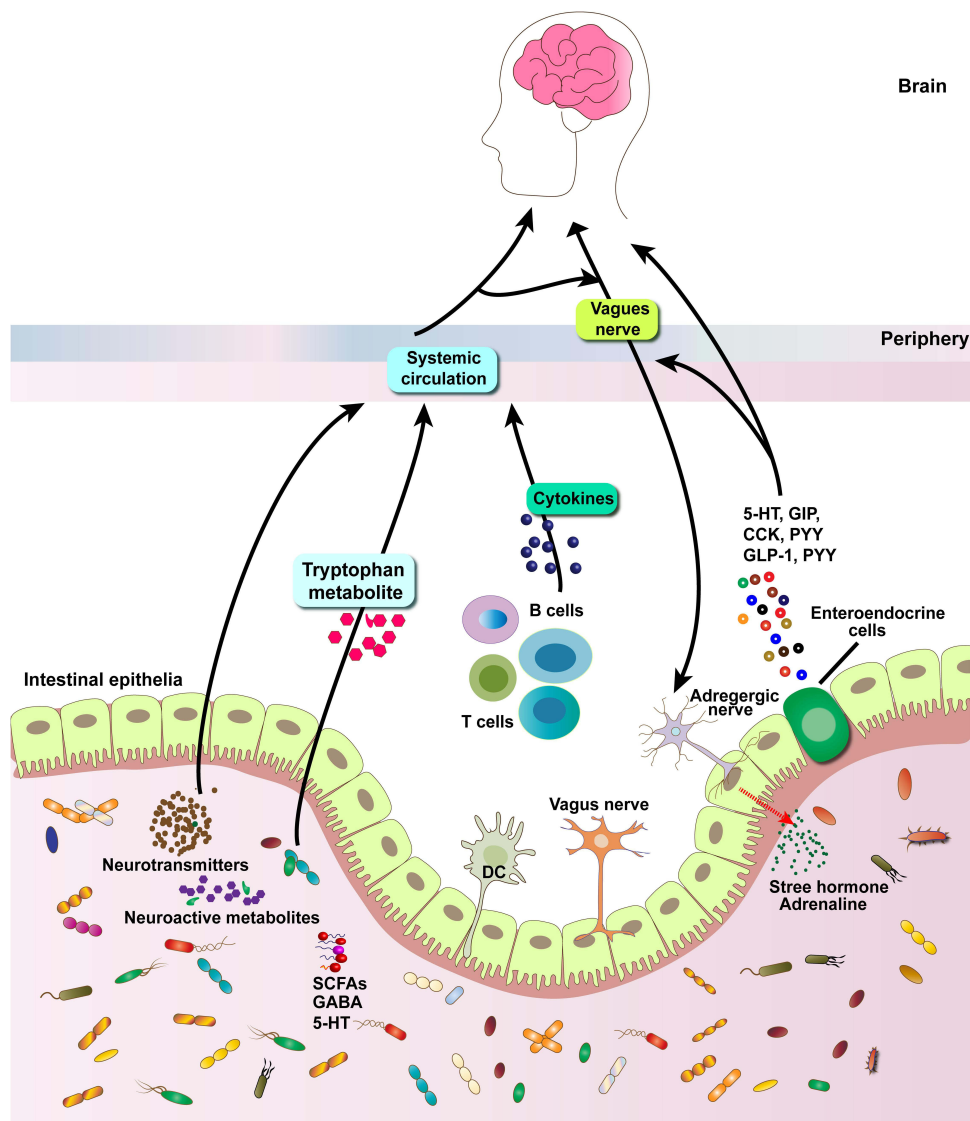


**Figure 1** Active role of gut microbiota in brain development. The gut microbiome plays a crucial role in various processes of brain development, such as the establishment of the blood-brain barrier (BBB), neurogenesis, myelination, microglia maturation, the development and maintenance of the microglial cells, the development of the HPA axis, and the stress response.

## Microbiome–Gut–Brain Axis (MGBA)

The gut and brain are important organs in the human body, with their own distinct anatomical locations, independent structures, and specific physiological functions.<sup>5</sup> However, they are regulated by several systems of the human body, influenced by the surrounding environment, and had a complete regulatory system.<sup>5</sup> The developing brain requires the availability of dietary components from the gut for the maturation and normal function of nerve cells. There is now clear evidence that gut microbes directly contribute to brain development and play an active role in neurodevelopmental processes (Figure 2) including, neurogenesis, microglia maturation and myelination. These processes are critical in shaping animal behavior and cognition.

The digestive tract, whose main task is to process ingested food and defend against invading microorganisms, as well as plays an important habitat for microorganisms, forming the “second gene pool” of the host and having a great impact on host health or disease.<sup>2,6</sup> The gut is home to a large number of regulatory cells of the host, such as nerve cells, immune cells and endocrine cells, being “second brain” of the host, with strong defensive and regulatory capabilities.<sup>6</sup> The functional activity of the brain is not only regulated by the nervous system, but also associated with the immune and endocrine systems.<sup>7</sup> Moreover, the brain is also influenced by the microorganisms colonized or invaded the host.<sup>4</sup> The general connection between gut and brain, termed the gut-brain axis (GBA), establishes neural and circulatory networks that enable mutual interaction, regulation and control.<sup>8</sup>



**Figure 2** Schematic diagram outlining known bi-directional communication pathways between the brain-gut-microbiome, including immunomodulatory responses, neuronal innervation, gut endocrine and microbial metabolite signaling. Short-chain fatty acids,  $\gamma$ -aminobutyric acid, 5-hydroxytryptamine, norepinephrine, and dopamine, such as SCFAs produced by many commensal bacteria, have this neuro-immunomodulatory role. Intestinal mucosal cells (green) contain more than 90% of the body's serotonin (5-HT).

**Abbreviations:** CCK, cholecystokinin; GLP-1, glucagon-like peptide-1; PYY, peptide YY; 5-HT, serotonin.

GM is classified as resident or transient microorganisms. Resident microorganisms are able to adhere and colonize the intestinal tract, and persist and multiply in the gut.<sup>9</sup> Passage microorganisms cannot adhere and colonize, and are easily carried away by feces.<sup>7</sup> The GM exchanges material, energy and information in the intestinal microenvironment.<sup>10</sup> Microorganisms accompany food into the gut, and they carry a large number of antigenic components, and produce a large number of metabolites.<sup>11</sup> Antigenic molecules are recognized by intestinal immune cells, and activated intestinal immune responses.<sup>12</sup> Some metabolites are able to cross the intestinal barrier, and reach the target cells through the intestinal neural or circulatory network, affecting the function of the host target organ.<sup>13</sup> GM play an important role in GBA by influencing the physiological functions of the gut and brain through multiple pathways, as well as being regulated by the gut and nervous system.<sup>14</sup> GM join the GBA as a foreign “biological organ” to form the MGBA (Figure 2).<sup>14,15</sup> Studies have shown that psychiatric disorders, such as depression, anxiety disorders, ASD, SCZ, and neurodegenerative pathologies including AD and PD, are associated with gut or GM<sup>4,16–18</sup>(Table 1).

**Table 1** Microbiota-Gut-Brain Axis Pathways and Neurological Disorders

Neurological Disorder	Pathways of the Gut Microbiota-Brain Axis	Studies in Animal Models	Studies in Humans
ASD	Metabolic and endocrine pathways	C57Bl/6j mice treated with p-Cresol <sup>19a</sup> In utero valproic acid mouse model of ASD <sup>20</sup> Maternal immune activation with poly(I:C) mouse model of ASD <sup>21</sup> BTBR T <sup>+</sup> Itpr3tf/J mouse model of ASD <sup>22,23</sup> Mice humanized with microbiota from individuals with ASD <sup>22</sup>	[24–28]
	Neuronal signaling	Shank3b <sup>-/-</sup> mouse model of ASD <sup>29,30</sup> In utero valproic acid and BTBR T <sup>+</sup> Itpr3tf/J mouse models of ASD <sup>29</sup>	Convincing evidence lacking in human studies
	Immune and neuroimmune pathways	Maternal immune activation with poly(I:C) mouse model of ASD <sup>21,31</sup>	Convincing evidence lacking in human studies
Neurodegenerative disorders	Metabolic pathways	Sod1 transgenic mouse model of amyotrophic lateral sclerosis <sup>32</sup> THY1- $\alpha$ Syn mouse model of PD <sup>33</sup>	[34–37]
	Neuronal signaling	6-Hydroxydopamine PD mouse model <sup>38</sup> Oral administration of <i>Proteus mirabilis</i> to C57Bl/6 mice <sup>39</sup> MitoPark PD mouse model <sup>40</sup>	[41,42] <sup>b</sup>
	Immune and neuroimmune pathways	Mice humanized with microbiota from individuals with multiple sclerosis <sup>43,44</sup> Oral administration of <i>P. mirabilis</i> to C57Bl/6 mice <sup>39</sup> Rag <sup>-/-</sup> and MOG transgenic mouse models of multiple sclerosis <sup>45</sup> HLA-DR3.DQ8 double-transgenic mouse model of multiple sclerosis <sup>46</sup> 5XFAD transgenic mouse model of Alzheimer disease <sup>47</sup> APPSWE/PS1 $\Delta$ E9 transgenic mouse model of Alzheimer disease <sup>48</sup> Rotenone-induced animal model of PD <sup>49</sup>	[49–52]
	Other microbial factors	THY1- $\alpha$ Syn mice model of PD <sup>33</sup> Fischer 344 rats and <i>Caenorhabditis elegans</i> <sup>53</sup>	Convincing evidence lacking in human studies
Mood disorders	Metabolic and endocrine pathways	Neonatal maternal separation in mice <sup>54</sup> Repeated psychosocial stress in mice <sup>55</sup> Unpredictable chronic stress in mice <sup>56</sup>	[57–60]
	Neuronal signaling	Dextran sodium sulfate colitis in mice <sup>61</sup> BALB/c mice <sup>62</sup> Neonatal maternal separation in mice <sup>63</sup>	[64,65]
	Immune and neuroimmune pathways	Rats humanized with depression patients' microbiota <sup>66</sup> Chronic mild stress in mice <sup>67</sup>	Convincing evidence lacking in human studies

**Notes:** <sup>a</sup>Observations based on preliminary data not yet peer-reviewed at the time of this publication. <sup>b</sup>Microbiota not implicated in these findings.

**Abbreviations:** ASD, autism spectrum disorder; MOG, myelin oligodendrocyte glycoprotein; PD, Parkinson disease; poly(I:C), polycytidylic acid;  $\alpha$ Syn,  $\alpha$ -synuclein.

## MGBA Communication Pathway

The mechanism of MGBA action, involving interactions among GM, the gut, and the brain, remains incompletely elucidated.<sup>68,69</sup> The MGBA is the interconnection among cell-cell, cell-microorganism, as well as the transport and effects of GM-derived bioactive molecules in the host body.<sup>70</sup> Physical barriers such as the intestinal epithelium and blood-brain barrier restrict direct microbial-host contact, necessitating chemical signaling via GM-derived molecules.<sup>71</sup> GM derived signaling molecule crossing the intestinal barrier acts directly on intestinal target cells, including peripheral neurons, intestinal immune cells, and intestinal endocrine cells, converting them into neural signals, immune signals, and endocrine signals and becoming pathways to regulate host target organs.<sup>14,72</sup> Accordingly, MGBA communication pathways are broadly classified into peripheral neural, immune, endocrine, and integrated communication pathways.<sup>73,74</sup> The GM affects the development and function of the brain through multiple pathways such as peripheral nerve, immune, and endocrine<sup>72,75</sup> (Table 2).

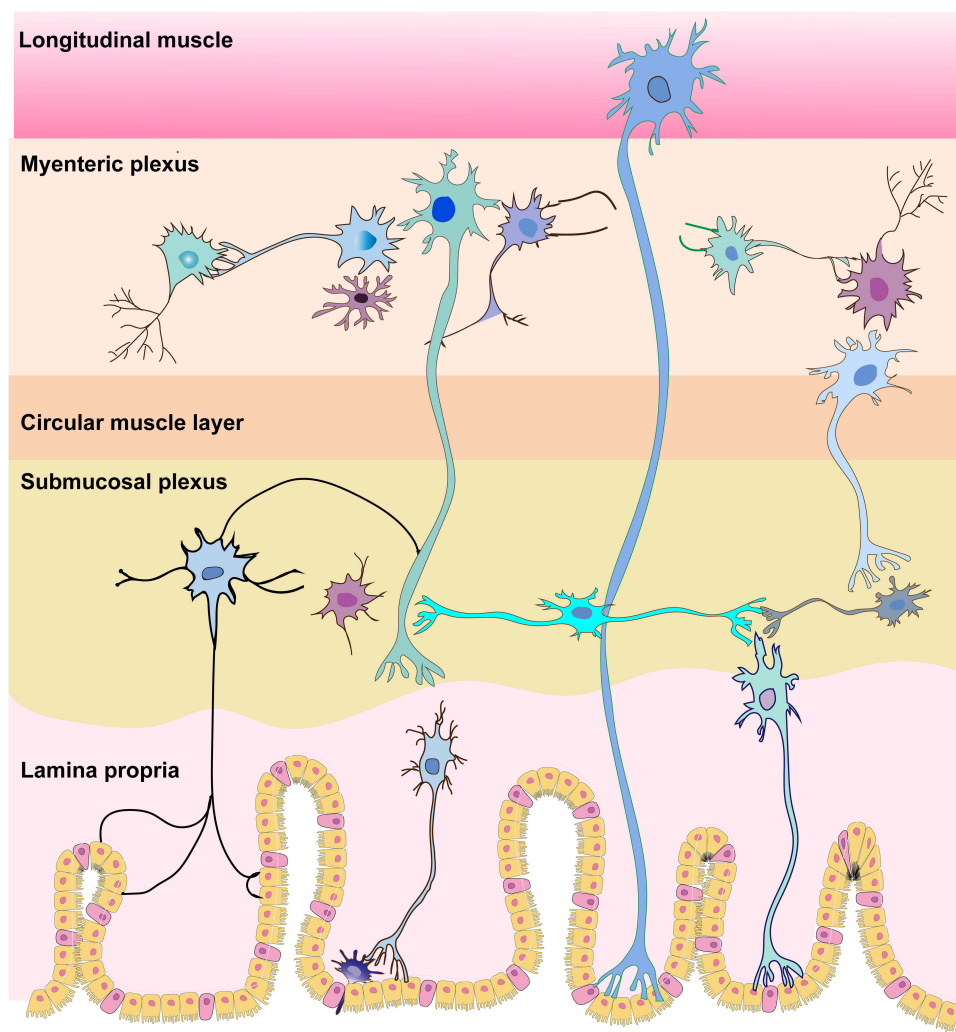
## Peripheral Nerve Communication Pathways

The gut's peripheral neural network comprises autonomic components (sympathetic and parasympathetic/vagal pathways) and the intrinsic enteric nervous system (ENS).<sup>6,93</sup> The centers of the ENS are located around the digestive tract (Figure 3). These low-level nerve centers regulate most of the physiological activities of the gut with a high degree of autonomy.<sup>93</sup> Their regulation is automated and mechanized, and occurred by “stress” and “emergency” responses.<sup>94</sup> The peripheral nerves of the gut cannot directly sense or regulate GM. However, the metabolites of GM contain

**Table 2** Roles of Gut Microbial Metabolites on Brain Development

Metabolites	Function	Ref.
Short-chain fatty acids (eg, butyric acid, propionic acid, acetic acid, valeric acid, isobutyric acid, isovaleric acid, and isocaproic acid)	Modulate BBB permeability; regulate microglia activation and neuroinflammation; regulate the activity of histone deacetylase	[16,76–78]
Amino acid metabolites (eg, GABA, serotonin, dopamine, “TRYP6”, norepinephrine, P-cresol)	Maintain normal neurotransmission and neurodevelopment; regulate the availability of vitamin B3 and NADP <sup>+</sup> in the brain; regulate neurotoxicity and neurodegeneration; regulate myelination and differentiation to oligodendrocytes; increase oxidative stress	[27,79–82]
Trimethylamine N oxide	Disturb mitochondria function; increase synaptic damage; promote neuroinflammation	[83–86]
Polyphenolic Metabolites	Modulate neuronal receptors; antioxidation; anti-inflammation	[87,88]
Bacterial Amyloid Proteins	Induce $\alpha$ -syn-aggregates in the brain; enhance neuroinflammation	[89,90]
Cholesterol Steroids hormones	Decarboxylation; dihydroxylation Deconjugations; oxidation reductions	[91,92]

**Abbreviations:** BBB, blood-brain barrier; GABA, gamma-aminobutyric acid; NADP<sup>+</sup>, nicotinamide adenine dinucleotide phosphate; “trypsin-6”, six tryptophan metabolism pathways generating neuroactive metabolites, including kynurenine, quinolinate, indole, indole acetic acid, and indole propionic acid.



**Figure 3** The distribution of the enteric neuronal network. The submucosal plexus, on the other hand, is located in the submucosal layer, where extrinsic sympathetic and parasympathetic fibers enter the entire layer of the intestinal wall and form a complex neural network with intrinsic enteric nerves and EGCs. The enteric neural network regulates enterocytes through neurotransmitters, neurotrophic factors and receptors.

neurotransmitters or neuromodulators, which act as important neural signaling molecules, and have effects on both the peripheral gut nerves and the brain<sup>6</sup> (Table 3).

GM metabolize tyrosine, tryptophan, and glutamate to produce a variety of important neurotransmitters, including dopamine, norepinephrine, 5-hydroxytryptamine (5-HT), and histamine.<sup>116,117</sup> Of these, acetylcholine and norepinephrine are the most important autonomic neurotransmitters.<sup>118</sup> Acetylcholine acts on nicotinic receptors in the cerebral cortex after being released from nerve endings.<sup>116</sup> The metabolism of tyrosine by GM produces precursors of 5-HT, which affects mental activity in the brain.<sup>119,120</sup> In addition, GM metabolites that enter the circulation can affect the blood brain barrier (BBB). Decreased levels of short-chain fatty acid (SCFA) may disrupt the integrity of the BBB.<sup>121,122</sup> Dietary supplementation with SCFA or SCFA-producing probiotic strains reverse the damage to the BBB, and maintain its integrity.<sup>121–124</sup>

The dense neural network of the gut is unable to directly contact the GM, but is able to sense some of the GM metabolite changes.<sup>125</sup> The vagus nerve (VN), which distributes large number of intestinal regulatory peptides and intestinal metabolite receptors, is the main pathway by which the GM influences the nervous system.<sup>126,127</sup> The VN is capable of transmitting information about gastrointestinal tract function and GM metabolites to the central autonomic network of the nervous system and brain through the intestinal visceral sensory afferent nerves.<sup>125,128</sup> After integrating the afferent information via the central nervous system (CNS), it affects the function of relevant target organs via efferent

**Table 3 | Gut Microbiota-Derived Neurotransmitters and Their Potential Functions in Brain Development**

Gut Microbiota	Neurotransmitters	Functions	Ref
<i>Staphylococcus Bacillus cereus</i> , <i>Proteus vulgaris</i> , <i>Serratia marcescens</i> , <i>Escherichia coli</i>	Dopamine	Affect immune cells, cytokines productions by activated T cells; regulate microglial cell migration	[95–99]
<i>Escherichia coli</i> , <i>Bacillus subtilis</i> , <i>Bacillus mycoides</i> , <i>Proteus vulgaris</i> , <i>Serratia marcescens</i>	Norepinephrine	Neuroprotective effects by suppressing inflammatory genes; modulate excitatory and interneuronal responses	[100–102]
<i>Lactobacillus Bifidobacterium</i> , <i>Streptococcus</i>	GABA	Modulate the inhibitory balance; cytokine downregulations by proinflammatory immune cells	[103–108]
<i>Candida</i> , <i>Streptococcus</i> , <i>Escherichia</i> , <i>Enterococcus</i> , <i>Pseudomonas</i>	Serotonin	Suppress MHC class II expression; reduce proinflammatory cytokines generated by macrophages and lymphocytes; development of enteric and CNS neurons	[109–115]

nerves.<sup>128,129</sup> In addition, intestinal VN can inhibit peri-intestinal inflammation and decrease intestinal permeability, and reduce the damage of GM and metabolites to the intestinal epithelial barrier.<sup>124,130</sup> Under stress, VN is inhibited and has deleterious effects on the intestinal epithelial barrier and GM, generating an excessive immune response to GM.<sup>130</sup> SCFA produced by GM metabolism acts as an informative molecule recognizing by VN receptors and having an activating effect on the VN.<sup>126</sup> Toll-like receptor 4 (TLR4) expressed on VN afferent fibers is also capable of recognizing GM-derived LPS, which influence brain function by the ENS or VN modulates intestinal permeability.<sup>49,129</sup>

## Immune Communication Pathways

GM carry large number of antigenic components that can be recognized by the receptors of intestinal immune cells.<sup>131,132</sup> Under physiological conditions, it can induce normal immune response and promote the establishment of intestinal immune function.<sup>8</sup> Under pathological condition, it can induce excessive immunity of intestinal mucosa and become an important pathogenesis of IBD.<sup>8,117,133</sup> Cytokines produced by activated immune cells can pass through the BBB and enter the brain, thus affecting the development and physiological activities of the host brain.<sup>134</sup> Activated intestinal immune cells can also enter the brain through the circulating network, affecting the immune function of microglia and astrocytes.<sup>117</sup> In addition, intestinal colonized GM can induce host immune tolerance and work with host immune cells to defend against exogenous pathogens through colonization resistance.<sup>8,132,134</sup>

## Endocrine Communication Pathways

The intestine is the largest endocrine organ in the human body, and enteroendocrine cells (EEC) constitute 1% of intestinal epithelial cells.<sup>135,136</sup> The endocrine cells of the intestinal mucosa gather abundant receptors on their surface, which can receive signaling molecules from various sources such as GM metabolites and cytokines, and regulate the hormone secretion of endocrine cells in a feedback manner.<sup>131,136</sup> Through the change of hormone level, it affects the function of target organs.<sup>131</sup> In addition, some GM metabolites can act on extraintestinal endocrine cells through blood circulation to regulate the secretion of specific hormones.<sup>133</sup> It has been found that GM metabolites can affect the secretion of 5-HT, substance P, cholecystokinin (CCK), gamma-aminobutyric acid (GABA) and other neuroactive mediators by enteroendocrine cells.<sup>116,117,119,120,137</sup> Another study has found that colonic L cells are able to receive indole metabolites produced by the metabolism of intestinal flora, affecting the secretion of glucagon-like peptide-1 (GLP-1), then stimulating colonic VN activity.<sup>138</sup>

## Integrated Communication Pathways

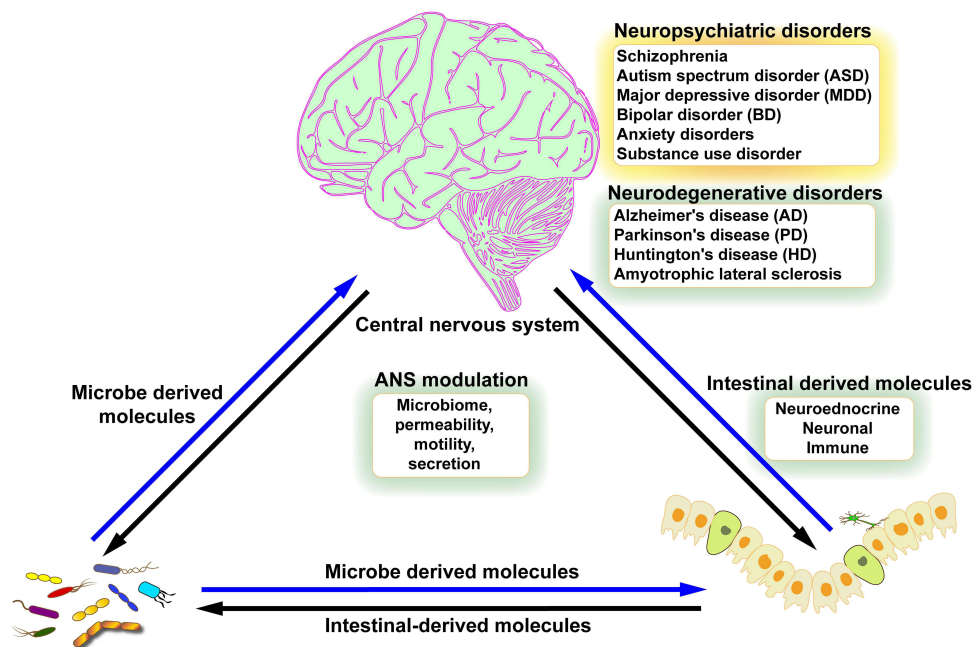
The regulatory systems of organs are complex and intertwined, and the communication pathway of MGBA may involve multiple regulatory systems such as neural, immune, and endocrine systems, forming a comprehensive communication pathway.<sup>69,73,139,140</sup> The hypothalamic–pituitary–adrenal (HPA) axis involves the nervous and endocrine systems, serving as a key integrative pathway within the MGBA.<sup>131,141</sup> Firstly, many hormones secreted by the HPA axis can directly regulate intestinal physiological functions and influence the composition of GM. Corticotropin releasing hormone (CRH) and glucocorticoids can also increase intestinal epithelial permeability and cause intestinal epithelial barrier dysfunction.<sup>140,142</sup> The dysfunction of the intestinal epithelial barrier can change the composition of GM and affect the balance of intestinal microecology.<sup>131,143</sup> Secondly, multiple metabolites of GM can activate the HPA axis, which in turn affects intestinal and brain function. SCFAs produced by gut bacteria can reduce the expression of genes encoding proteins involved in the HPA axis and can also activate the HPA axis by releasing lipopolysaccharides and peptidoglycan.<sup>144</sup> *Escherichia coli* (*E. coli*) can produce Clp- $\beta$  proteins that mimic  $\alpha$ -melanocortin ( $\alpha$ -MSH) to stimulate the release of Melanocortin precursor, which promotes the synthesis of Adrenocorticotrophic hormone (ATCH).<sup>145–147</sup> The metabolites of GM can influence the secretion of neuroactive mediators by enteroendocrine cells, including 5-HT, substance P, growth inhibitor, CCK, GABA, adenosine triphosphate (ATP), leptin, and orexin.<sup>141,142</sup> These mediators can influence peri-intestinal nerve and brain function, exhibiting a cascading effect of GM on endocrine cells and neurons.<sup>141,144</sup>

## Study on the Correlation Between GM and IBD

MGBA plays an important role in the pathogenesis and disease activity of IBD. GM disorders are the most important exogenous cause of IBD, and IBD patients are almost always accompanied by GM changes<sup>2,132,148–150</sup> (Figure 4).

## Studies on the Effect of GM Disorders on IBD

GM disorders affect intestinal peristalsis, disrupt the intestinal barrier, and lead to recurrent intestinal infections and abnormal intestinal immunity, which plays an important role in the pathogenesis and disease activity of IBD.<sup>151</sup> GM carries antigenic components that may cause abnormal intestinal immunity.<sup>151</sup> GM metabolites can also be involved in



**Figure 4** Systems biology model of brain-gut-gut microbiota interactions. The gut microbiota communicates with the gut connectome via microbial metabolites, and changes in gut function can affect the gut microbiota. In the presence of disturbances such as psychosocial stress, alterations in the gain of these two-way interactions can change the stability and behavior of the system, manifesting as brain-gut disturbances.

the pathogenesis of IBD through neurological, immunological, endocrine, and other regulatory pathways causing intestinal dysfunction and disruption of the intestinal barrier.<sup>152</sup> It has been found that butyrate is a SCFA produced by intestinal microbial metabolism, which provides energy to promote the production of mucin and adenosine monophosphate of colonic cells, and shape the mucosal immune system by regulating the differentiation of relevant T cells.<sup>152,153</sup> Thibault et al found that the number of some butyrate-producing bacteria and the amount of butyrate were reduced in Ulcerative colitis (UC) patients, reflecting the effect of GM metabolites on IBD.<sup>153,154</sup> Therefore, regulating GM disorders has become an important target for IBD treatment.<sup>155,156</sup> Probiotic supplementation and fecal microbiota transplantation (FMT) are commonly used in the treatment of clinical IBD, and their safety and efficacy have been recognized.<sup>156–158</sup> Indirectly, this reflects the important role of GM disorders in IBD pathogenesis and disease activity.<sup>2</sup>

## Study of GM Changes in Patients with IBD

It has been found that IBD patients suffer from intestinal microecological imbalance accompanied by a decrease in the diversity and abundance of the bacterial flora.<sup>151</sup> For instance, there was a decrease in the number of intestinal commensal bacteria, such as *Bacteroides* and *Firmicutes*, and an increase in the number of harmful bacteria, such as *Aspergillus phylum* and *Actinomycetes phylum*.<sup>152</sup> Common causative organisms of intestinal infections present in patients with IBD include *Clostridium difficile* (*C. difficile*), *Campylobacter spp.*, adherent-invasive *E. coli*, and *Salmonella spp.*<sup>153</sup> There are also studies on the intestinal flora during the active phase of IBD that found a significant increase in the number of bacteria such as *Enterobacteriaceae*, *Enterococci*, *yeasts*, *Bacteroides*, and *Peptococcus*, and a significant decrease in the number of bacteria such as *Lactobacillus*, *Fusobacterium*, and *Bifidobacterium* in the colon, as compared to the remission phase.<sup>153,154</sup> In addition, the intestinal fungal community of IBD patients had an altered compositional structure with increased diversity and abundance as well as elevated intestinal mucosal colonization density compared to the healthy population.<sup>155,156</sup> The intestinal viral community of IBD patients had an increased diversity of viruses as well as an increased chance of intestinal viral infections compared to the healthy population.<sup>2</sup> Whether changes in the intestinal fungal and viral communities are associated with the pathogenesis of IBD remains to be studied in depth.<sup>156–158</sup>

## Study on the Correlation Between GM and Neuropsychiatric Disorders

Depression, anxiety, ASD, SCZ, PD, AD and other neuropsychiatric disorders are affected by MGBA.<sup>7,68</sup> GM can interfere with the development of the brain, and affect the physiological functions of the brain.<sup>4</sup> There is a distant distance between GM and the brain, and the metabolites of GM and the brain also have intestinal barriers, blood-brain barriers, needing to use the neural and circulatory network in order to reach the brain.<sup>141,142</sup> The main mutual communication between GM and the brain pathway is the peri-intestinal nerves, which combine with the immune system or endocrine system to establish an integrated communication pathway between GM and the brain.<sup>159,160</sup> For example, in the HPA axis, GM-derived signaling molecules influence brain function through endocrine organs and central nervous system transit<sup>151</sup> (Table 4).

## GM and Depression or Anxiety

Emotion is a higher function of the brain with relatively independent functional areas.<sup>170</sup> It is generally accepted that the emotional region of the cerebral cortex is in the prefrontal lobe, and subcortical emotional centers include the hypothalamus, limbic system, and brainstem network structures.<sup>170,171</sup> Depression or anxiety both manifest as emotional disorders and they often occur together.<sup>172,173</sup> The main features of depression are depressed mood and loss of interest, while anxiety disorders are characterized by mood anxiety and panic attacks.<sup>173</sup> They can be accompanied by emotional experiences such as guilt, despair, worry, and irritability.<sup>173,174</sup> The pathogenesis of depression and anxiety is unclear and influenced by individual health and illness, as well as by external factors, such as social and environmental factors.<sup>174</sup> GM also plays an important role in the development of host affective disorders.<sup>145</sup>

It has been found that germ-free mice attenuate stress responses in the HPA axis and less depressive-like behaviors than normal mice.<sup>140,141</sup> Implantation of fecal bacteria from depressed patients increased the incidence of depressive

**Table 4** Study on the Correlation Between Gut Microbiota (GM) and Neuropsychiatric Disorders

Diseased State	No. of Diseased vs Healthy	Shift in Flora	Method Used	Outcome	Ref.
ASD	33 autistic/7 sibling controls/8 nonsibling controls	↑ <i>Bacteroidetes</i> , <i>Desulfovibrio</i> species and <i>Bacteroides vulgatus</i> in severely autistic group, ↑ <i>Firmicutes</i> in control group	Bacterial tag-encoded FLX amplicon pyrosequencing (bTEFAP)	Firmicutes and Bacteroidetes showed most difference	[161]
ASD	40 ASD patients/40 healthy subjects	↑ <i>Firmicutes/Bacteroidetes</i> , <i>Collinsella</i> , <i>Dorea</i> , <i>Corynebacterium</i> , <i>Candida</i> and <i>Lactobacillus</i> ↓ <i>Alistipes</i> , <i>Parabacteroides</i> , <i>Bilophila</i> , <i>Dialister</i> and <i>Veillonella</i> Constipated autistic individuals had ↑ <i>Escherichia/Shigella</i> and <i>Clostridium cluster XVIII</i>	Bacterial 16S rRNA gene (V3–V5 hypervariable regions) and fungal internal transcribed spacer (ITS1 rDNA region) amplification and 454 pyrosequencing	Altered gut microbial community associated with ASD, not depending by the constipation status of autistic individuals rather by autistic disorder itself	[162]
ASD	21 autistic subjects/19 children without autism	↑ <i>Burkholderia</i> ↓ <i>Neisseria</i> , two <i>Bacteroides</i> species and <i>Escherichia coli</i>	16S rRNA gene (Tagencoded FLX amplicon) pyrosequencing and disaccharidase activity via biochemical assays	Positive correlation between abundance of <i>Clostridium</i> species and disaccharidase activity	[163]
ASD	45 ASD children/45 neurotypical children	↓ <i>Acidaminococcaceae</i> , <i>Lachnospirillum</i> , <i>Tyzzera</i> subgroup 4, <i>Flavonifractor</i> and unidentified <i>Lachnospiraceae</i>	Bacterial 16S ribosomal RNA (V3–V4 hypervariable regions) gene sequencing	Less diversity and richness of gut microbiota in ASD group than the neurotypical group	[164]
PD	72 PD patients/72 controls	↓ <i>Prevotellaceae</i> , ↑ <i>Enterobacteriaceae</i> and <i>Ruminococcaceae</i>	Pyrosequencing of bacterial 16S rRNA (VI–V3 regions) gene	Altered intestinal microbiome in PD is related to the motor phenotype	[165]
PD	89 PD patients/66 controls	↑ <i>Christensenella</i> , <i>Oscillospira</i> , <i>Catabacter</i> , <i>Lactobacillus</i> and <i>Bifidobacterium</i> ↓ <i>Bacteroides</i> , <i>Dorea</i> , <i>Prevotella</i> and <i>Faecalibacterium</i>	16S rRNA (V3–V4 regions) sequencing performed on a MiSeq platform (Illumina)	This triggers aggregation of asynuclein and generation of Lewy bodies	[166]
[PD]	52 PD patients/36 healthy controls	↑ <i>Lactobacillus</i> ↓ <i>Clostridium coccoides</i> , <i>C. leptum</i> and <i>Bacteroides fragilis</i>	Quantitative RT-PCR of 16S or 23S rRNA	Due to dybiosis worsening of constipation leads to progression of PD	[50]
PD	38 PD patients/34 controls	↑ <i>Betaproteobacteria</i> , <i>Ralstonia</i> , <i>Akkermansia</i> , <i>Verrucomicrobia</i> , <i>Oscillospira</i> , <i>Bacteroides</i> and <i>Oxalobacteraceae</i> ↓ <i>Faecalibacterium</i> , <i>Firmicutes</i> , <i>Coprobacillaceae</i> , <i>Dorea</i> , <i>Erysipelotrichi</i> , <i>Faecalibacterium</i> , <i>Clostridia</i> , <i>Blautia</i> , <i>Coproccoccus</i> and <i>Roseburia</i>	High-throughput rRNA (V4 variable region) gene amplicon sequencing	Increased LPS biosynthesis and type III bacterial secretion systems in PD patients with altered microbiota trigger inflammation induced misfolding of α-Syn	[35]

(Continued)

Table 4 (Continued).

Diseased State	No. of Diseased vs Healthy	Shift in Flora	Method Used	Outcome	Ref.
PD	34 PD patients/34 controls	↓ <i>Faecalibacterium prausnitzii</i> , <i>Lactobacillaceae</i> , <i>Bacteroidetes</i> , <i>Prevotellaceae</i> and <i>Enterococcaceae</i> ↑ <i>Enterobacteriaceae</i> , <i>Akkermansia muciniphila</i> and <i>Bifidobacterium</i>	Real-time quantitative PCR using an ABI PRISM 7900HT sequence detection system	Microbial dysbiosis cause reduction in SCFAs producing alterations in ENS and contribute to GI dysmotility in PD	[37]
AD	25 AD patients/25 controls	↓ <i>Firmicutes</i> and <i>Bifidobacterium</i> ↑ <i>Bacteroides</i>	16S rRNA (V4 region) gene sequencing	Corelationship between level of differentially abundant genera and CSF biomarkers	[167]
AD	43 AD patients/43 controls	↓ <i>Bacteroidetes</i> , <i>Bacteroidia</i> , <i>Lachnospiraceae</i> , <i>Negativicutes</i> , <i>Bacteroidaceae</i> and <i>Veillonellaceae</i> ↑ <i>Bacilli</i> , <i>Actinobacteria</i> , <i>Ruminococcaceae</i> , <i>Lactobacillaceae</i> and <i>Enterococcaceae</i>	16S rRNA (V3–V4 region) sequencing	AD might not be a disease of brain itself, and brain health is closely associated with our whole body	[168]
AD	24 AD patients/33 having other than classic dementia/51 controls	↑ <i>Alistipes</i> , <i>Bacteroides</i> , <i>Barnesiella</i> and <i>Odoribacter</i> ↓ <i>Barnesiella</i> , <i>Eubacterium</i> , <i>Roseburia</i> and <i>Lachnoclostridium</i>	Metagenomic sequencing	Frailty and malnutrition are related to dementia	[169]

symptoms in mice compared to implantation of normal human fecal bacteria.<sup>57</sup> Aizawa et al found that the intestinal probiotic levels of *Bifidobacterium* and *Lactobacilli* were significantly lower in patients with major depression than in healthy individuals.<sup>175,176</sup> Patients with major depression had an increased diversity of fecal flora, with an increase in *Aspergillus* and *Actinobacteria* and a decrease in the abundance of the thick-walled phylum, such as *Bacteroides*.<sup>176</sup> Patients had a higher abundance of pro-inflammatory bacteria in the gut, such as *Enterobacter*, whereas SCFA-producing bacteria were reduced in abundance, such as *Fecal bacilli* and *fecal cocci*.<sup>176–178</sup> These metabolite changes may lead to intestinal immune dysfunction.<sup>179</sup>

GM and GM metabolites affect the emotional function areas of the brain through neural, immune, and endocrine pathways, resulting in affective disorders such as depression or anxiety.<sup>174,180</sup> Human mood is regulated by important neurotransmitters such as dopamine and 5-HT, while GM has an important influence on the biosynthesis of dopamine and 5-HT.<sup>119,120</sup> GM disorders affect the synthesis of dopamine and 5-HT, which has an impact on the regulation of mood and makes it easy to develop symptoms of depression or anxiety.<sup>116,119</sup> It was found that protein or messenger ribonucleic acid (mRNA) expression of brain-derived neurotrophic factor was reduced in a mouse model of intestinal inflammation, and anxiety-like behavior was increased in mice.<sup>120,181</sup> Their anxiety behaviors were normalized after probiotic treatment, which suggests that the state of intestinal inflammation is associated with anxiety-like behavior, and can be improved by regulating GM disorders.<sup>181</sup> It has been shown that GM dysbiosis is an important trigger of intestinal inflammation, and the resulting increase in pro-inflammatory cytokines promotes the risk of depression or anxiety

symptoms in humans.<sup>182–184</sup> Another experiment found that pretreatment with probiotics reduced c-fos proto-oncogene protein (C-FOS) expression and increased brain-derived neurotrophic factor (BDNF) expression in different regions of the brain in rats under stress, as a result, the abnormal proliferation and morphological changes of neurons in the hippocampus could be avoided.<sup>182,184</sup>

## GM and ASD

ASD is a group of neurodevelopmental disorders. The main manifestations are different degrees of behavioral stereotypes, language developmental disorders and social disorders.<sup>185,186</sup> The etiology of ASD is not known, and mainly related to genetic variations, neurodevelopmental disorders, immune dysfunction and other factors.<sup>187</sup> Studies have shown that GM may affect the onset and course of ASD, and intervening in GM disorders can improve the clinical symptoms of ASD, making it a potential target for ASD treatment.<sup>188,189</sup>

It was found that reduced social motivation and interest in novelty can be improved in germ free (GF) mice after colonization with gut bacteria.<sup>190</sup> Suggesting a role for GM in regulating social interactions and interest.<sup>188</sup> Additionally, the GM composition and metabolites were significantly altered in children with ASD, mainly by a decrease in the number of *Bacteroides* and a decrease in the ratio of *Bacteroides* to *thick-walled bacteria*, and an increase in the number of *Lactobacillus*, *Clostridium*, *Desulfovibrio* and *Enterobacter*.<sup>188,191–193</sup> *Bifidobacterium* are among the earliest probiotics to colonize the neonatal gut, and their reduced abundance may affect neurodevelopment and contribute to the pathogenesis of ASD.<sup>194</sup> Plasma metabolites (including nicotinamide ribose, Inosine 5'-Monophosphate (IMP), iminodiacetate, methyl succinate, galacturonate, valerylglycine, sarcosine, and leucylglycine) levels were significantly reduced in a study that accurately assessed plasma metabolites in children with ASD.<sup>194</sup> The study found that *C. difficile*, through its metabolite propionic acid, can trigger ASD in rats.<sup>191,195</sup> Treatment of *Clostridium intestinalis* infections with antibiotics, such as vancomycin, significantly improved psychiatric symptoms in children with ASD.<sup>194,196</sup> Treatment of refractory *C. difficile* infections with fecal transplants has been shown to improve psychiatric symptoms in children with ASD.<sup>197,198</sup> A study in a mouse model of ASD showed that treatment with *C. difficile* improved small intestinal osmolarity, altered the composition of the GM, and alleviated ASD-related symptoms.<sup>195,199</sup> Another study showed that mice transplanted with fecal flora from ASD patients showed changes in blood and fecal GM metabolites, and exhibited ASD-like behavioral deficits.<sup>190</sup> The ASD-like behavioral defects in some mice can be ameliorated by supplementation with probiotics or metabolites.<sup>190,200</sup>

## GM and SCZ

The main characteristic of SCZ is that the individual's way of perceiving reality is severely impaired and he or she experiences persistent psychological and behavioral difficulties.<sup>201,202</sup> Clinical manifestations include persistent delusions and hallucinations, disorganized thinking and behavior, which may be accompanied by anxiety, depression, social withdrawal, aggressive violence, and suicidality.<sup>203,204</sup> The etiology and pathogenesis of SCZ have not been elucidated. It is currently believed that SCZ is related to the individual's genetics, brain development and structure, psychological cognition, and behavioral stress, as well as social, environmental, and other external factors.<sup>203,204</sup> Many studies suggest that GM may influence the onset and course of SCZ.<sup>201,205</sup>

The most frequently reported changes in GM composition in SCZ patients were *Clostridium*, *Enterococcus*, *Prevotella*, and especially increased abundance of *Lactobacillus spp.*<sup>4,206,207</sup> The intestinal flora of SCZ patients contained a wide range of parthenogenetic anaerobes, such as *Lactobacillus fermentum*, *Enterococcus faecalis*, and *alkalophilic bacillus*, which are rare in the intestinal tracts of healthy individuals.<sup>208,209</sup> Through macro-genomic sequencing and 16s ribosomal RNA (rRNA) sequencing, it has been found that the GM composition of SCZ patients shows higher  $\alpha$ -diversity at the genus level and higher  $\beta$ -diversity at the species level compared to controls.<sup>200,210</sup> It has also found that glutamate synthase (GOGAT) is more active in the intestines of SCZ patients than that in healthy controls, which correlated with GM-associated intestinal IgA levels.<sup>208,211,212</sup>

Studies have found that GF mice are less likely to develop SCZ symptoms than normal mice.<sup>208</sup> SCZ-related behaviors can be induced in GF mice by transplantation of SCZ patient feces, accompanied by altered levels of glutamate, glutamine, and GABA in the hippocampus, but could not be identified to be associated with a specific

intestinal bacterial strain.<sup>213</sup> Some studies have found that microbial infections during fetal life may increase the risk of developing SCZ in children, but have not delved into which specific pathogenic microbial infections.<sup>214,215</sup> Animal studies have found that rodents with an altered gut core microbiome after treatment with sub-chronic phenacyclidine (sub-PCP) can produce SCZ-like symptoms.<sup>216</sup>

## GM and AD

AD is a neurodegenerative disease that occurs in the brain and manifests itself as a combined impairment of cognitive content and skills, accompanied with a decline in behavioral abilities.<sup>217,218</sup> The etiology of AD is complex and unknown, with more than 30 possible influencing factors and hypotheses.<sup>219</sup> In terms of pathogenesis, the more accepted hypotheses include  $\beta$ -amyloid (Ap) deposition, tau protein hyperphosphorylation, and abnormal glucose metabolism in the brain caused by insulin resistance.<sup>220</sup> Many studies have shown that GM play an important role in various hypotheses of AD pathogenesis.<sup>221–223</sup>

Animal studies have found that GF mice have a lower incidence of AD compared to conventionally raised mice from the same background.<sup>222</sup> Amyloid plaques and neuroinflammatory manifestations were not seen in the brain tissue of GF mice, which showed GM played an important role in the pathogenesis of AD.<sup>224,225</sup> Clinical studies have found differences in the GM composition of AD patients compared to the healthy population. The richness and diversity of GM was reduced in AD patients compared to the healthy population, with a decrease in the *Firmicutes*, *Bifidobacterium*, and an increase in the *Bacteroides*.<sup>226–228</sup> One controlled study found a significant increase in the abundance of *Escherichia* and *Shigella*, which was involved in the inflammatory response, in fecal samples from AD patients.<sup>168</sup> GM alterations were found to be closely associated with pathological deposition of Ap and hyperphosphorylation of tau proteins.<sup>229,230</sup> GM metabolites, such as short-chain fatty acids, can interfere with Ap deposition and help prevent AD.<sup>76,123</sup>

## GM and PD

PD is also a neurodegenerative disease that occurs in the brain, manifested by impairment of the brain's motor regulatory function and movement disorders, such as resting tremor and bradykinesia, which may be accompanied by non-motor symptoms including sensory disturbances, psychosomatic disorders, and gastrointestinal dysfunction.<sup>231,232</sup> The main pathological feature of PD is the deposition of  $\alpha$ -synuclein ( $\alpha$ -syn) and aggregation of Lewy bodies in dopaminergic neurons in the dense nigral region of the midbrain, contributing to neuronal degeneration and death as well as significant reduction of dopamine content in the striatum.<sup>232,233</sup> The exact etiology of the pathological changes associating with PD is unclear, and genetic factors, environmental factors, ageing, and oxidative stress may be involved.<sup>234</sup> Many studies have shown that GM influences the pathologic process of PD through metabolites.<sup>70,235</sup>

Several studies have found significant alterations in GM and metabolites in PD mouse models and PD patients compared to healthy controls.<sup>235,236</sup> This was mainly characterized by increased abundance of *Lactobacillus* and decreased abundance of *Prevotella* and *Puccinia spp.*<sup>235,237</sup> Studies of GM composition in PD patients have revealed a decrease in SCFA-producing intestinal strains such as *Prevotellaceae*, *E. faecalis*, and *Gastric cocci*, a decrease in intestinal strains with anti-inflammatory effects such as *Coprococcus*, and *E. faecalis*, and an increase in bacteria involved in lipid metabolism and in increasing intestinal permeability.<sup>236</sup> It has also been observed that changes in GM metabolites such as SCFA and lipopolysaccharide (LPS) may influence the onset or development of PD.<sup>34,238</sup> Some studies have found that the deposition of  $\alpha$ -synuclein in the ENS cause by abnormal intestinal barrier function and GM disorders may be correlated with the pathogenesis of PD.<sup>215,239</sup> It has been pointed out that bacterial neurotoxins, such as LPS, enter the bloodstream through the disrupted intestinal epithelial barrier, and produce inflammatory cytokines by immune cells through nuclear factor kappa-B (NF- $\kappa$ B) and TLR4, leading to systemic inflammatory responses.<sup>49,240</sup> Moreover, bacterial LPS and inflammatory cytokines (including TNF- $\alpha$ , IL-1 $\beta$ , and IL-6) can induce BBB destruction, causing  $\alpha$ -syn accumulation in dopaminergic neurons in the substantia nigra.<sup>241,242</sup>

## Correlation Studies of IBD and Neuropsychiatric Disorders

IBD is often accompanied by neuropsychiatric disorders, and MGBA may be a link by which they establish a connection.<sup>243,244</sup> This connection is mainly manifested in comorbidities and it is difficult to clarify that there is a causal relationship between them.<sup>132,149,245</sup> The gut is distant from the brain and various physiologic barriers exist.<sup>246</sup> However, pathological changes such as inflammatory response, barrier disruption, and intestinal microecological disorders occurring in IBD can send signals to the brain through the peripheral nerves, the immune system, or the endocrine system, affecting the brain's regulatory or higher neural functions.<sup>246,247</sup> In turn, the brain affects the structure and function of the gut by regulating the nervous system, immune system or endocrine system, which is an important pathogenesis of IBD.<sup>245,248</sup>

### IBD with Anxiety or Depression

Studies have shown that there is a significant increase in the prevalence of depression and anxiety in people with IBD compared to the general population, especially during the active phase of IBD.<sup>150,249</sup> The correlation between IBD and anxiety or depression is significantly higher compared to other chronic diseases such as hypertension and diabetes.<sup>250</sup> There is a high prevalence of symptoms of anxiety and depression in patients with IBD, with up to a third of patients affected by anxiety symptoms and a quarter affected by depression symptoms.<sup>251</sup> Prevalence was also increased in patients with active disease: half of these patients met criteria for anxiety symptoms and a third met criteria for depression symptoms.<sup>250,252</sup>

GM is a target of MGBA and has become an important target for IBD treatment.<sup>239,253</sup> Studies have found that treatment targeting GM can improve IBD symptoms.<sup>249,250</sup> And with the improvement of IBD symptoms, patients' depression or anxiety symptoms also improved significantly. Some studies have reported that medication for IBD also has a palliative effect on anxiety or depression.<sup>250,254</sup> It is not clear whether this palliative effect is associated with remission of IBD or if it is simply a medication effect.<sup>249</sup> Anxiolytic or antidepressant therapy for people with IBD has also been shown to be helpful in the remission of IBD.<sup>249,255</sup> Addressing psycho-spiritual disorders in patients with IBD can improve their compliance and satisfaction with treatment and enhance the outcome of IBD.<sup>249,255</sup> Other studies have shown that antidepressant or anxiety medications can relieve IBD symptoms or reduce the risk of IBD recurrence and improve quality of life, but evidence that can be characterized is lacking.<sup>255,256</sup>

### IBD with ASD

A meta-analysis showed that the prevalence of gastrointestinal dysfunction was significantly higher in children with ASD than in healthy children.<sup>194</sup> Gastrointestinal symptoms in children with ASD may also be related to the severity of ASD.<sup>257,258</sup> Some studies have shown that about 40% of ASD patients have experienced gastrointestinal disorders, and both psychiatric and gastrointestinal symptoms in ASD patients have been associated with GM disorders.<sup>259</sup> One study found that children with ASD are often diagnosed with co-occurring disorders including IBD, suggesting a strong association between ASD and IBD.<sup>260,261</sup> Another study found that interventions targeting GM improved IBD symptoms and was also able to alleviate psychiatric symptoms of ASD.<sup>262</sup> And targeting ASD alone was observed to alleviate gastrointestinal symptoms as well as alter GM composition in patients with IBD.<sup>194,261</sup>

### IBD with AD or PD

For patients with IBD, screening for AD or PD has found that IBD modestly increases the risk of developing AD or PD.<sup>149,263</sup> Dietary factors and gastrointestinal dysfunction are correlated with the onset and progression of AD or PD.<sup>149</sup> Patients with AD or PD are also frequently associated with gastrointestinal dysfunction, which may be an influential factor in the pathogenesis of IBD.<sup>149,264</sup> Both IBD and AD or PD are associated with MGBA, a common pathway for their correlative linkage.<sup>149</sup> Studies have shown that GM plays a key role not only in the pathogenesis of IBD, but also in the pathogenesis of AD or PD.<sup>265,266</sup> Studies have shown that treatments targeting intestinal infections, microecological imbalances, and intestinal dysbiosis may also affect neurological symptoms of AD or PD.<sup>267</sup> Early anti-inflammatory therapies for IBD may reduce the risk of developing AD or PD.<sup>72</sup> Intervening in GM disorders in patients with IBD may

be an early preventive measure to reduce the risk of developing AD/PD by altering intestinal permeability, modulating inflammatory responses, and reducing the aggregation of  $\alpha$ -synuclein in the ENS.<sup>72,268</sup>

## The Role of the GM in IBD and Neuropsychiatric Disorders

The clinical translation of MGBA focuses on GM applications in the diagnosis and treatment of IBD and neuropsychiatric disorders.<sup>11</sup> In terms of diagnosis, current studies have identified abnormalities in GM composition and its metabolites of IBD and neuropsychiatric disorders.<sup>68,267</sup> However, these abnormalities lack specificity and sensitivity, and are difficult to assist in the diagnosis of IBD and neuropsychiatric disorders.<sup>18,68</sup> Therapeutically, intervening in GM disorders has achieved better results in IBD treatment, whereas therapeutic research in neuropsychiatric disorders is still in the beginning stage.<sup>11,155</sup> Using GM as a therapeutic target, it will intervene in the GM through gut microecological modifiers, GM transplantation, dietary modification and drug selection, and explore the therapeutic effects of these interventions on IBD or neuropsychiatric disorders, respectively.<sup>11,72,157</sup>

## Intestinal Microecological Regulators

Gut microecology is a dynamic community of GM and the environment in which they live. Foreign microorganisms are constantly introduced with food, and intestinal microorganisms are constantly excreted with feces.<sup>269–271</sup> It is also influenced by the host's genetics, immunity, age, diet, medication, and gastrointestinal dynamics in a state of dynamic change.<sup>272</sup> The maintenance of a long-term and stable coexistence between the GM and the host is called intestinal microecological equilibrium.<sup>273</sup> Dysbiosis refers to the disruption or transformation of this coexistence.<sup>272</sup> Gut microecological regulators can correct the intestinal microecological imbalance to a certain extent and increase beneficial intestinal microorganisms.<sup>158,274,275</sup> Gut microecological regulators include probiotics, prebiotics and synbiotics.<sup>272</sup>

### Probiotics

The vast majority of gut microorganisms are bacteria.<sup>276</sup> Intestinal flora can be categorized into beneficial, neutral and harmful bacteria according to their relationship with the host.<sup>276,277</sup> Probiotics are selected from beneficial bacteria or strains of bacteria, cultured in vitro to make food or drugs, and after taking them, they can go through the test of gastric acid and bile to reach the intestinal colonization.<sup>278,279</sup> At present, the probiotics used in human body mainly include *Lactobacillus*, *Bifidobacterium*, *Enterococcus*, *Streptococcus*, *Bacillus*, *Clostridium*, and *Saccharomyces*.<sup>277,280</sup>

Intestinal colonized probiotics form a microbial film on the surface of the intestinal mucosa have colonization resistance (CR) effect, such as inhibiting the growth and activity of pathogenic bacteria, enhancing mucosal immunity, and maintaining the intestinal mucosal barrier.<sup>278</sup> Intestinal probiotics can exert anti-inflammatory effects and reduce gastrointestinal symptoms in IBD subjects through CR effects.<sup>281</sup> Rembaeken et al randomized 83 patients with active UC after remission induced by standard treatment to mesalazine or *E. coli Nissle*, and found that there was no statistically significant difference between the two groups in the rate of UC recurrence.<sup>281,282</sup> Lichtenstein et al found that VSL#3 enriched with eight probiotic species, including *Saccharomyces boulardii*, were useful in maintaining clinical remission in patients with Crohn's disease (CD).<sup>283,284</sup>

Certain strains of enteric bacteria have also been shown to be effective in improving behavioral symptoms of neuropsychiatric disorders such as anxiety and depression, ASD, AD, and PD, and are referred to as "psychotropic probiotics".<sup>285,286</sup> "Psychotropic probiotics" are part of the probiotic family, which can obtain psychotropic benefits, such as anti-anxiety and anti-depression by influencing the host's mood, cognition and other mental activities.<sup>286</sup> Several preclinical studies and clinical reports on *Bifidobacterium spp.* and *Lactobacillus spp.* have found that supplementation with these two "psychotropic probiotics" improves mood, reduces anxiety, and enhances cognitive function, which can significantly improve CNS function and alleviate psychiatric symptoms.<sup>287,288</sup> *Lactobacillus spp.* and *Bifidobacterium spp.* as probiotics can alleviate PD-related symptoms.<sup>289</sup> *Bacillus spp.* as probiotics have the ability to convert L-tyrosine to L-DOPA, thus improving dopamine production and secretion, and relieving PD-related symptoms.<sup>290</sup> In addition, probiotics are able to reduce the levels of pro-inflammatory factors in the body, such as IL-6, IL-1 $\beta$ , TNF- $\alpha$ , and microglia activation markers, suggesting that they have the ability to reduce the overall level of inflammation.<sup>291</sup> Targeting the GM with probiotics becomes a possible treatment for a variety of neuropsychiatric disorders.<sup>286</sup>

## Prebiotics

Prebiotics are substances that are not digested by the gastrointestinal tract, but selectively become “food” for one or a few beneficial intestinal bacteria, stimulating the growth and activity of the beneficial bacteria.<sup>292,293</sup> Prebiotics only selectively stimulate the growth of beneficial bacteria and do not promote the growth of harmful bacteria, and do not increase the digestive burden of the gastrointestinal tract and its nutritional needs.<sup>294</sup> The most basic prebiotics are carbohydrates, which can be derived from food or formed when food is refined and processed.<sup>292</sup> Currently, commonly used prebiotics include oligofructose, oligogalactose, oligosaccharides, and isomaltooligosaccharides.<sup>292</sup> The combined preparation of probiotics and prebiotics is called symbiotic.<sup>295,296</sup> It is a new generation of microecological regulator, which plays the physiological functions of probiotics and prebiotics at the same time, so that probiotics and prebiotics can coordinate their effects, fight against diseases together and maintain the microecological balance of the organism.<sup>297,298</sup>

A meta-analysis showed that prebiotics can significantly reduce the intestinal mucosal injury score and improve the index of intestinal inflammatory response in a rat model of IBD.<sup>296</sup> Drablińska et al found that inulin, which is rich in oligofructose, can improve the metabolism of amino acids in the plasma and urine of children with CD, and maintain intestinal permeability, thus mitigate the gastrointestinal symptoms of children with CD.<sup>299</sup> It has been found that prebiotics containing galactose and oligofructose exerts antidepressant and anxiolytic effects, which can reverse depression or anxiety symptoms triggered by chronic stress.<sup>300</sup> Prebiotics with N-acetylcysteine administered for 8 weeks can reduce irritability and repetitive behaviors in infants with ASD compared to controls.<sup>301</sup> Another study has also shown that lactulose-containing prebiotics can ameliorate cognitive deficits through autophagic and anti-inflammatory pathways in AD mouse models.<sup>302</sup>

## FMT

FMT involves transferring a healthy human fecal sample carrying intestinal flora and metabolites into a patient’s intestine to re-establish normal functioning intestinal flora in the treatment of intestinal and extra-intestinal diseases.<sup>303</sup> Fecal samples can be infused directly into the patient’s colon via colonoscopy, enema, or made into lyophilized material for oral feeding.<sup>304,305</sup> FMT ensures the integrity and bioactivity of the intestinal flora, and the quantity and quality of bacteria reaching the intestine.<sup>306</sup> FMT makes it easier to establish the structure of the healthy intestinal flora or model the intestinal flora of a specific disease.<sup>305</sup> Clinically, FMT has been shown to be effective in the treatment of recurrent and refractory *C. difficile* infections (CDI).<sup>304,305,307,308</sup> FMT application in IBD treatment has also resulted in significant clinical remission.<sup>305</sup> There is also a large body of research exploring the FMT use in the treatment of other intestinal and non-intestinal related diseases. Study has shown that FMT can improve the diversity of the GM and alleviate gastrointestinal symptoms.<sup>306</sup> Patients with a variety of neuropsychiatric disorders, including anxiety and depression, ASD, and PD, also benefit from FMT treatment, with no serious adverse events occurring during treatment or during follow-up.<sup>309</sup>

One study conducted in vitro culture of GM transplantation in ASD mice, which resulted in a significant reduction of anxiety-like behavior in mice.<sup>310</sup> FMT treatment in AD mice by enema can change the composition of the GM in mice, and thus effectively alleviated the cognitive dysfunction of AD, which indirectly showed that changes in the composition of the GM relating to cognitive dysfunction.<sup>311</sup> In another study, FMT was performed by colonoscopy on ASD patients, and the GM of ASD patients was transformed to a healthy state, and the ASD-related symptoms of patients were significantly improved.<sup>195</sup> However, more relevant studies are still needed to demonstrate the effect of FMT on ASD patients.<sup>312</sup>

## Dietary Modification

Diet is the main source of nutrients for the GM and a pathway for invasion by foreign microorganisms.<sup>313</sup> Different dietary structures carry different bacterial species and nutritional elements that have a direct impact on GM. Studies have found that gut microecology can be altered by dietary modifications.<sup>313,314</sup> Westernized diets and ketogenic diets lack carbohydrates available to gut microbes, leading to a decrease in gut microecological diversity.<sup>315–317</sup> Vegetarian diets and Mediterranean diets with adequate dietary fiber intake are effective in improving the diversity and stability of gut microecology.<sup>318</sup>

The aim of regulating intestinal microecological imbalance and combating MGBA-associated diseases is achieved through the development of a rational and individualized dietary regimen that alters intestinal microbial composition and metabolites.<sup>314,315,319</sup> It has been found that a vegetarian diet or the addition of SCFA to the diet will increase the level of Unified Parkinson's Disease Rating Scale (UDPRS III) and reduce the effective daily dose of levodopa equivalents, a potentially effective non-pharmacological treatment for PD.<sup>320</sup> It has been shown that breastfeeding for 6 months reduces the chances of ASD manifestation, while formula feeding is associated with increased *C. difficile* abundance in the gut.<sup>321</sup>

## Drug Use

Chemical drugs can also affect GM parasitized in the human body, causing intestinal microecological imbalance and associated diseases.<sup>322</sup> Conversely, GM also affects host metabolism and absorption of chemical drugs.<sup>323,324</sup> The interactions between chemical drugs and gut microbes need to be taken into account when using chemical drugs, such as antibiotics, immunomodulators, anticancer and antipsychotic drugs.<sup>325</sup> In a large-scale, in vitro screening study of more than 1000 drugs against 40 representatives of gut commensals, it was found that 24% of the drugs tested exhibited growth inhibition against at least one bacterial strain.<sup>326</sup>

Antibiotics can directly affect the gut microflora, potentially eliminating pathogenic bacteria as well as depleting probiotics.<sup>323</sup> For intestinal infections, the pros and cons need to be weighed and assessed individually to rationalize the choice of antibiotics in the clinic.<sup>322</sup> Both pathogenic and probiotic bacteria should be eliminated to avoid intestinal microecological imbalance. Rifaximin is an orally non-absorbable antibiotic.<sup>327</sup> Prantera et al showed that rifaximin induced remission of moderately active CD with low side effects.<sup>328</sup> Rifaximin achieves its therapeutic effect in IBD mainly through local anti-infective and repair of intestinal epithelial barrier damage in the gastrointestinal tract, but large-scale clinical trials are still needed to confirm this.<sup>329,330</sup>

A significant negative correlation was found between some antipsychotic drugs and microbial diversity, especially antidepressants and antipsychotics had the highest correlation.<sup>331,332</sup> Selective 5-hydroxytryptamine reuptake inhibitors (SSRIs), such as fluoxetine, sertraline, and citalopram, have shown some antimicrobial activity against strains of *Bacillus*, *Clostridium*, *Enterococcus*, *Pseudomonas*, and *Staphylococcus*.<sup>326,333</sup> It has been found that the tricyclic antidepressant amitriptyline has antimicrobial activity against intestinal pathogenic bacteria, such as *Bacillus spp.*, *Staphylococcus spp.* and *Vibrio cholerae*.<sup>334</sup> Promethazine exerts growth inhibition against *Yersinia pestis* and *E. coli*, which can cause intestinal infections.<sup>335</sup>

## Conclusions and Perspectives

IBD and neuropsychiatric disorders exhibit strong associations with the MGBA, both characterized by distinct GM alterations.<sup>72</sup> GM dysbiosis is recognized as a key contributor to IBD pathogenesis and is implicated in the neurobiological pathways underlying psychiatric disorders.<sup>11</sup> Current interventions targeting gut dysbiosis—including probiotics, FMT, and dietary modulation—demonstrate moderate efficacy in IBD (clinical remission rates 40–60%) and emerging potential in neuropsychiatric disorders (eg, 30% reduction in depression scores).<sup>336</sup> A clear causal relationship between IBD and neuropsychiatric disorders is difficult to establish based on current research. However, IBD and neuropsychiatric disorders have a significantly higher chance of co-occurring with each other, increasing each other's incidence and prevalence to varying degrees.<sup>268</sup> They have also demonstrated a reciprocal and mutually reinforcing effect in treatment, mainly in terms of interventions on intestinal microecology.<sup>268</sup> In terms of clinical translation, it is still difficult to assist in the diagnosis of IBD and neuropsychiatric diseases due to the technical limitations of gut microbiological testing and the lack of gut microecological alterations with high specificity and sensitivity. In terms of therapeutic transformation, intestinal microecological regulators are abundant and diverse, including probiotics, prebiotics, synbiotics, and postbiotics, which are able to regulate GM composition and metabolites more accurately. The technologies of donor screening, bacterial fluid preparation, and transplantation pathway for FMT have matured, and are gradually expanding the scope of clinical application and standardizing the criteria for clinical application. Many studies have shown that GM has emerged as a therapeutic target for IBD and a potential therapeutic target for neuropsychiatric disorders.

GM in the host intestine is large in number and diverse, and affected by multiple factors such as host diet, medication, and health, disease. There are still great challenges in GM detection techniques and research methods. Macroscopic correlation studies have failed to adequately take into account the complex changes and interfering factors of GM, and homogenization and standardization are difficult to achieve. Evidence for the existence of correlation between GM and neuropsychiatric disorders is still insufficient. Microcosmic correlation studies are still scarce, and more studies at the molecular level are needed to explore the extent and mechanisms of correlation. Moreover, while therapeutic of the GM holds transformative potential, critical challenges impede clinical translation. Standardization hurdles, prebiotics lack dose-response consensus and FMT protocols vary dangerously in donor screening, processing, and delivery routes. Patient heterogeneity introduces further complexity—baseline microbiome architecture of FMT responsiveness, while host genetics reduce probiotic engraftment. Long-term efficacy remains precarious due to ecological succession dynamics. In the future, it is necessary to continuously improve the detection technology of GM, conduct extensive experimental comparative studies, and continuously explore the pathways and effect mechanisms of MGBA. It will be more reliable to verify the correlation between GM and specific diseases and promote the clinical translation of MGBA in IBD and neuropsychiatric diseases.

## Abbreviations

5-HT, 5-hydroxytryptamine; AD, Alzheimer's disease; Ap,  $\beta$ -amyloid; ASD, autism spectrum disorder; ATP, adenosine triphosphate; BBB, Blood Brain Barrier; BDNF, Brain-derived neurotrophic factor; CCK, cholecystokinin; CD, Crohn's disease; *C. difficile*, *Clostridium difficile*; CDI, Clostridium difficile infections; C-FOS, c-fos proto-oncogene protein; CNS, central nervous system; CR, colonization resistance; CRH, corticotropin releasing hormone; EEC, enteroendocrine cells; ENS, enteric nervous system; *E. coli*, *Escherichia coli*; FMT, fecal microbiota transplantation; GABA, gamma-aminobutyric acid; GBA, Gut-brain axis; GF, germ free; GLP-1, glucagon-like peptide-1; GM, gut microbiota; GOGAT, Glutamate synthase; HPA, hypothalamic-pituitary-adrenal axis; IMP, Inosine 5'-Monophosphate; IBD, Inflammatory bowel disease; IL-1 $\beta$ , interleukin-1 $\beta$ ; IL-1 $\beta$ , interleukin-1 $\beta$ ; IL-6, interleukin-6; L-DOPA, 3,4-Dihydroxyphenyl L-Alanine; LPS, lipopolysaccharide; mRNA, messenger ribonucleic acid; MGBA, microbiome-gut-brain; NF- $\kappa$ B, nuclearfactor $\kappa$ B; PD, Parkinson's disease; rRNA, ribosomal RNA; SCFA, short-chain fatty acid; SCZ, schizophrenia; SSRIs, Selective 5-hydroxytryptamine reuptake inhibitors; subPCP, subchronic phencyclidine; TLR4, Toll-like receptor 4; TNF- $\alpha$ , tumor necrosis factor- $\alpha$ ; UC, Ulcerative colitis; UDPRS III, Unified Parkinson's Disease Rating Scale; VN, vagus nerve;  $\alpha$ -MSH, mimic alpha melanopsin;  $\alpha$ -syn,  $\alpha$ -synuclein; Ap,  $\beta$ -amyloid.

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas, took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published, have agreed on the journal to which the article has been submitted, and agree to be accountable for all aspects of the work.

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No conflicts of interest, financial or otherwise, are declared by the authors.

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