

# Fecal Microbiota Transplantation in Autism Spectrum Disorder

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**Abstract:** Autism spectrum disorder (ASD) is a group of neurodevelopmental disorders that begin in infancy. In recent years, the incidence of ASD in the world is increasing year by year. At present, the etiology and pathogenesis of ASD are not clear, and effective treatments are still lacking. In addition to neurobehavioral symptoms, children with ASD often have obvious gastrointestinal symptoms. Gut microbiota is a large microbial community in the human gut, which is closely related to the nervous system and can affect brain development and behavior through the neuroendocrine, neuroimmune and autonomic nervous systems, forming a microbiota-gut-brain axis connection. Recent studies have shown that children with ASD have significant gut microbiota and metabolic disorders, and fecal microbiota transplantation (FMT) is expected to improve ASD-related symptoms by regulating gut microbiota and metabolism. This review paper will therefore focus on FMT in the treatment of ASD, and FMT is effective in improving gastrointestinal and neurobehavioral symptoms in children with ASD.

**Keywords:** autism spectrum disorder, fecal microbiota transplantation, gastrointestinal symptoms, gut microbiota, microbiota-gut-brain axis

## Introduction

Autism spectrum disorder (ASD) is a group of multifactorial neurodevelopmental disorders characterized by verbal communication deficiency, social interaction impairment, restricted interests and repetitive behaviors.<sup>1</sup> At present, the etiology and pathogenesis of ASD are not clear.<sup>2</sup> In recent years, the incidence of ASD in the world is increasing year by year. For the one in 100 children affected worldwide,<sup>3</sup> progress in the treatments of ASD has been frustratingly slow and effective treatments are still lacking.<sup>4</sup> Children with ASD are at least three times more likely to experience co-occurring gastrointestinal symptoms, including constipation, diarrhea and abdominal pain, than neurotypical children.<sup>5</sup>

Recent studies have confirmed differences in the composition of gut microbiota between ASD patients and neurotypical people.<sup>6</sup> Microbial communities play a central role in the maturation and development of the immune, neural and gastrointestinal systems and are also responsible for important metabolic pathways.<sup>7</sup> A bidirectional connection exchanges information between gut microbiota and central nervous system. Therefore, the microbiota-gut-brain axis plays an important role in ASD and has been proposed as a target for treatment of ASD.<sup>8,9</sup> Fecal microbiota transplantation (FMT) refers to the introduction of fecal microbiota from a healthy donor into the gastrointestinal tract of a patient. In recent years, FMT is a novel and adequate approach to alter the host gastrointestinal microbial ecosystem.<sup>10</sup> Evidence indicates that gut microbiota are involved in several neurological diseases, for including ASD, parkinson's disease, alzheimer's disease, epilepsy, multiple sclerosis, Tourette's syndrome, Guillain-Barre syndrome and diabetic neuropathy, and FMT may be a potential treatment option.<sup>11-13</sup>

Although FMT had been used in ASD, the available evidence is still insufficient, with limited studies conducted or ongoing in human studies. Large double-blind randomized controlled trials are needed to further elucidate the effect of FMT in ASD.<sup>14-17</sup> This review paper will therefore focus on FMT in the treatment of the core behavioral symptoms and

gastrointestinal symptoms of ASD, by beginning with describing the gut microbiota changes observed in ASD patients and the involvement of microbiota-gut-brain axis in several neurological diseases, then examine the studies of FMT conducted in animals and patients with ASD, and determine that FMT is effective in improving gastrointestinal and neurobehavioral symptoms in children with ASD.

## Autism Spectrum Disorder and Gut Microbiota

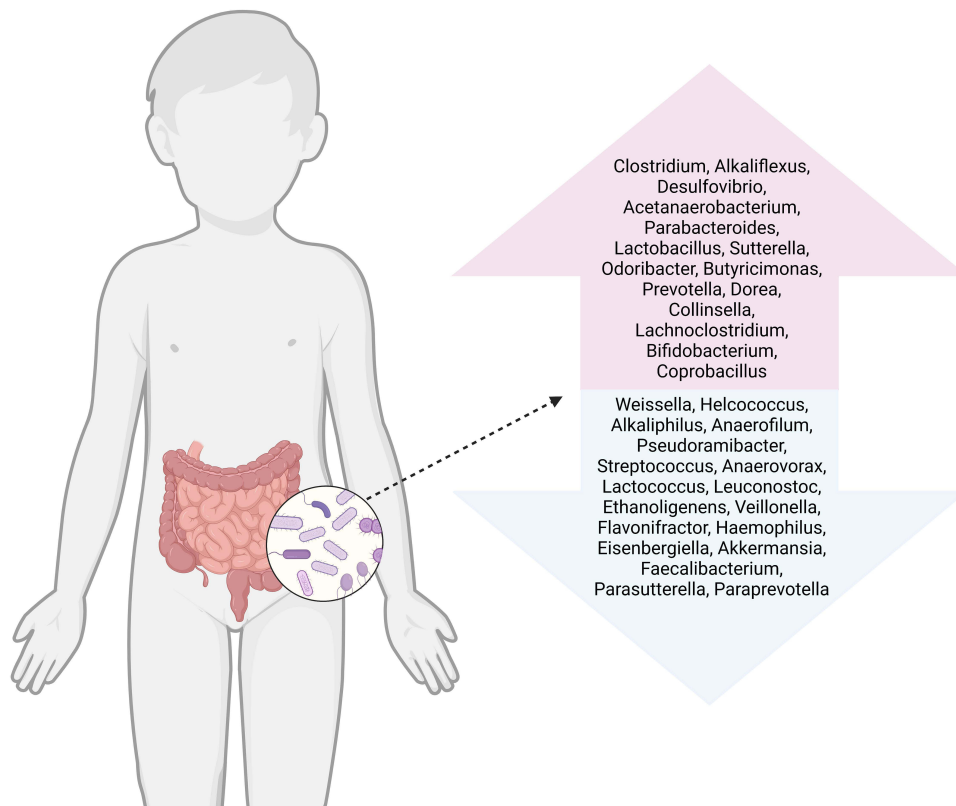
Gastrointestinal symptoms are common in individuals with ASD, but the underlying mechanisms remain unclear.<sup>18</sup> Changes in the gut microbiota may be involved in the pathogenesis of gastrointestinal symptoms in children with ASD, including significant increases in the relative abundance of *Actinobacteria* and *Proteobacteria*.<sup>19</sup> Compared with neurotypical children, the development of gut microbiota in children with ASD was relatively stagnant and gradually deviated from the normal track. There was no significant change in alpha diversity with age in children with ASD, the early microbiota was unstable and immature and the common bacteria was difficult in colonization. The microbiome relationship significantly altered before 3 years old in children with ASD, which is consistent with their nodes at which behavioral deficits occur. The changes of microbial function and bacterial relationship were correlated with the severity of neurobehavioral and gastrointestinal symptoms.<sup>20</sup>

The changes of gut microbiota and metabolites in the blood of children with ASD are summarized (Table 1). The most striking finding was the complete absence of non-sporogenic anaerobes and microaerophiles in the neurotypical children, while the children with ASD had significant numbers of these bacteria.<sup>21</sup> Compared with the neurotypical children, the phylum level of *Verrucomicrobia* decreased in autistic children.<sup>22</sup> *Betaproteobacteria* and *Clostridiales* increased from the class level and order level respectively. *Selenomonadales* and *Bacteroidales* decreased from the order level.<sup>23</sup> From the family level, *Erysipelotrichaceae* and *Ruminococcaceae* was higher, and *Prevotellaceae*, *Actinomycetaceae*, *Coriobacteriaceae*, *Oscillospira*, *Streptococcaceae*, *Bifidobacteriaceae* were lower in children with ASD.<sup>24,25</sup> From the genus level (Figure 1), *Clostridium*, *Alkaliflexus*, *Desulfovibrio*, *Acetanaerobacterium*, *Parabacteroides*, *Lactobacillus*, *Sutterella*, *Odoribacter*, *Butyricimonas*, *Prevotella*, *Dorea*, *Collinsella*, *Lachnoclostridium*, *Bifidobacterium*, *Coprobacillus* elevated, and *Weissella*, *Helcococcus*, *Alkaliphilus*, *Anaerofilum*, *Pseudoramibacter*, *Streptococcus*, *Anaerovorax*, *Lactococcus*, *Leuconostoc*, *Ethanoligenens*, *Veillonella*, *Flavonifractor*, *Haemophilus*, *Eisenbergiella*, *Akkermansia*, *Faecalibacterium*, *Parasutterella*, *Paraprevotella* reduced in children with ASD.<sup>26–28</sup> *Clostridium bolteae*, *Bacteroides vulgatus* and *Faecalibacterium prausnitzii* were higher from the species level in autistic children than neurotypical children.<sup>29</sup> Elevated amounts of GABA, serotonin, lipopolysaccharides and p-cresol were also found in the blood of children with ASD,<sup>30–33</sup> while the amount of homocysteine, methionine, glutathione, S-adenosylmethionine,<sup>33</sup> arachidonic acid, docosahexaenoic acid and eicosapentaenoic acid<sup>34</sup> decreased. More evidence show that microbiological changes in autistic children with gastrointestinal symptoms are associated with digestive enzyme deficiency,<sup>35</sup> poor carbohydrate absorption,<sup>36</sup> selective diet,<sup>37</sup> increased bacterial toxins,<sup>38</sup> and neuro-inflammatory signaling alteration.<sup>39</sup> Microbiota related metabolic disorder may be involved in the pathogenesis of gastrointestinal symptoms in patients with ASD. Differential metabolites are involved in the metabolism of several

**Table 1** Elevated and Decreased Gut Microbiota and Metabolites in the Blood of Children with ASD

Change	Phylum	Class	Order	Family	Species	Metabolites in the Blood
Elevated	NA	<i>Betaproteobacteria</i> <sup>23</sup>	<i>Clostridiales</i> <sup>23</sup>	<i>Ruminococcaceae</i> , <i>Erysipelotrichaceae</i> <sup>24,25</sup>	<i>Clostridium bolteae</i> , <i>Bacteroides vulgatus</i> , <i>Faecalibacterium prausnitzii</i> <sup>29</sup>	GABA, Serotonin, Lipopolysaccharides, p-cresol <sup>30–33</sup>
Decreased	<i>Verrucomicrobia</i> <sup>22</sup>	NA	<i>Selenomonadales</i> , <i>Bacteroidales</i> <sup>23</sup>	<i>Prevotellaceae</i> , <i>Actinomycetaceae</i> , <i>Coriobacteriaceae</i> , <i>Oscillospira</i> , <i>Streptococcaceae</i> , <i>Bifidobacteriaceae</i> <sup>24,25</sup>	NA	Homocysteine, Methionine, Glutathione, S-adenosylmethionine, Arachidonic acid, Docosahexaenoic acid, Eicosapentaenoic acid <sup>33,34</sup>

Abbreviation: NA, not available.



**Figure 1** Gut microbiota changes in ASD patients at the genus level. Many studies have shown that the composition of gut microbiota altered in ASD patients. The genus level inside the upward arrow were higher in the ASD patients than those in neurotypical patients. On the contrary, the genus level inside the downward arrow were lower (Figure created with BioRender.com).

neurotransmitters, such as serotonin, dopamine, histidine and gamma-aminobutyric acid.<sup>29</sup> Overproduction of pathogenic bacteria or reduction of probiotics can lead to gut microbiota disturbance, mediating a variety of neurological and psychological diseases.<sup>40</sup> On the whole, normal gut microbiota plays an important role in maintaining stable gut-brain axis function.

## Microbiota-Gut-Brain Axis

The microbiota-gut-brain axis consists of complex network and multiple pathways that allow signals to be sent between the microbiota and the brain.<sup>41</sup> The microbiota also regulates sensory processing, social behavior and stress responses directly or indirectly through a variety of neural activities and signaling molecules.<sup>42</sup> Conversely, the brain can directly regulate the composition and function of gut microbiota by releasing neuroactive compounds that act on certain gut microbial receptors, or indirectly by regulating the motility and secretory activity of the gut.<sup>43</sup>

Gut microbiota ferment dietary fiber to produce short-chain fatty acids (SCFAs), and transform tryptophan (TRP) in protein foods into metabolites with different functions in the host body. SCFAs such as acetate, butyrate and propionate can increase the expression of claudin and occludin, thereby reducing the blood-brain barrier permeability. SCFAs and TRP metabolites block the activation of transcription factors in astrocytes and microglia by blocking proinflammatory factors, leading to cerebral homeostasis.<sup>44</sup> Recent studies have suggested that gut microbiota metabolites, such as propionic acid and butyrate can have effects on mitochondrial activity in lymphoblastoid cell line from children with ASD.<sup>45,46</sup> 4-cresol produced by *clostridium difficile* can affect GABAergic and glutamate transport, causing neurological and physiological changes in patients with ASD.<sup>47,48</sup>

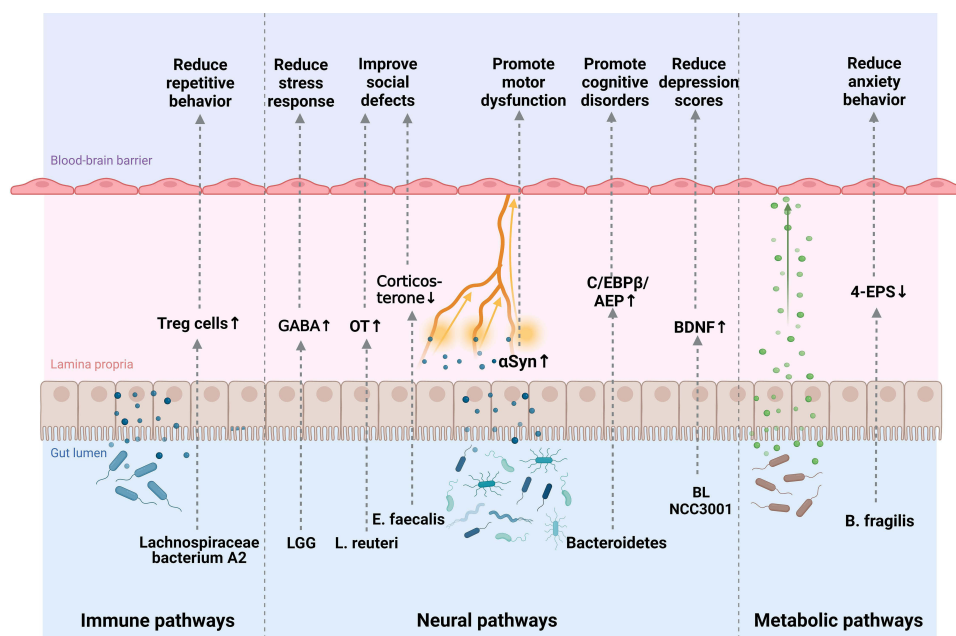
Gut microbiota affects brain development and neurobehavior through immune, neural and metabolic pathways.<sup>18</sup> Key findings of the pathways involved in the pathophysiology of several neurological and psychological diseases are summarized (Figure 2). In the animal studies of ASD, the relative abundance of *Lachnospiraceae bacterium A2* was

associated with reduced repetitive behavior and increased Treg cells in mesenteric lymph nodes.<sup>49</sup> *Lactobacillus reuteri* (*L. reuteri*) acts on the vagus nerve and restores social-induced synaptic plasticity in the ventral tegmental region of the midbrain. *L. reuteri* could increase the level of oxytocin (OT) and affect oxytocin-dopamine system to improve the social defects in mice. *L. reuteri* was ineffective in mice lacking oxytocin receptors.<sup>50</sup> *Enterobacter faecalis* (*E. faecalis*) reduced corticosterone levels in stressed mice by inhibiting activation of the HPA axis, influencing social behavior in mice through neuronal circuits that mediate the stress response in the brain.<sup>51</sup>

Some patients with ASD also have similar symptoms such as anxiety, depression and motor dysfunction. In the studies of depression and anxiety, mice fed with *Lactobacillus rhamnosus* (*L. rhamnosus*) showed less emotional stress and anxiety, with elevated level of gamma-aminobutyric acid (GABA) mRNA expression in the hippocampus.<sup>52</sup> The metabolite 4-EPS produced by the gut microbiota of mice was absorbed into the blood and circulated through the whole body into the brain, influencing the complex behavior of mice by affecting the formation of myelin sheath in the brain. 4-EPS promoted the anxiety behavior of mice and *Bacteroides fragilis* (*B. fragilis*) probably alleviate the process.<sup>53</sup> In a pilot study conducted in patients with irritable bowel syndrome, *Bifidobacterium longum* NCC3001 (*BL NCC3001*) played a role in decreasing depression scores and improving the quality of life by upregulating the level of brain derived neurotrophic factor (BDNF) in the hippocampus probably.<sup>54</sup>

In the studies of neurodegenerative disorder, the  $\alpha$ -synuclein ( $\alpha$ Syn) accumulates in the intestinal nervous system and travels to the brain via the vagus nerve, causing neurodegeneration and motor dysfunction. Gut microbiota from patients with Parkinson's disease enhanced motor dysfunction in mice, indicating that changes in the gut microbiota could influence motor deficits.<sup>55</sup> The Bacteroidetes raised the metabolism of the pro-inflammatory polyunsaturated fatty acid by activating the C/EBP $\beta$ /AEP pathway, which enhanced microglial cell activation and neuroinflammation, and promotes pathological and cognitive disorders of Alzheimer's disease.<sup>56</sup> These classic pathways in the microbiota-gut-brain axis can be further explored in the study of ASD.

In the studies of ASD-related genes, animal studies have shown that EPHB6 deficiency mediates autism-like behavior in mice by inducing gut microbiota dysregulation, which leads to vitamin B6 and dopamine deficiency, and thereby induces



**Figure 2** The microbiota-gut-brain axis in neurological and psychological diseases. The microbiota-gut-brain axis mainly includes three pathways of interaction: immune, neural and metabolic pathways. These pathways can be involved in the pathophysiology of ASD, depression, anxiety, Parkinson's disease and Alzheimer's disease. *Lachnospiraceae bacterium A2* increase Treg cells and reduce repetitive behavior. *L. rhamnosus* reduce stress and anxiety by elevating GABA mRNA expression level. *L. reuteri* increase OT to improve social defects. *E. faecalis* reduce corticosterone by inhibiting the HPA axis.  $\alpha$ Syn in the intestinal nervous system travels to the brain via the vagus nerve. *Bacteroidetes* promote motor dysfunction by activating the C/EBP $\beta$ /AEP pathway. *BL NCC3001* decrease depression scores by upregulating BDNF. *B. fragilis* promote anxiety behavior through 4-EPS. (Figure created with BioRender.com).

excitatory or inhibitory imbalance of pyramidal neurons in the prefrontal cortex through the dopamine D1 receptor pathway.<sup>57</sup> In *Drosophila melanogaster*, loss of KDM5 function resulted in impaired intestinal barrier function, dysbiosis with intestinal microecology, and abnormal social behavior. KDM5 protein is a histone demethylase that regulates innate immune signaling and bacterial disturbances. The social behavior, longevity and cellular phenotype of *Drosophila* with KDM5 protein deficiency were partially saved by antibiotic treatment or feeding *Lactobacillus plantarum*.<sup>58</sup>

## FMT Studies in ASD Animal Models

FMT studies in ASD animal models were summarized (Table 2). Transplanting gut microbiota from ASD or typically-developing donors into germ-free mice showed that colonization with gut microbiota of ASD patients was effective to induce signature ASD behaviors.<sup>59</sup> It has been reported that the ASD mouse models can be established from the offspring by repeatedly transplanting fecal extract of children with ASD into pregnant mice.<sup>60</sup>

**Table 2** FMT Studies in ASD Animal Models

Ref.	Design	Pre-FMT	FMT	Follow-Up	GI Outcomes	Neurobehavioral Outcomes	Microbiota Changes	Adverse Effects
Sharon et al, 2019, USA <sup>59</sup>	3 offspring groups of mice with FMT from ASD and TD children: 1.mild ASD-FMT, 2. ASD-FMT, 3. TD-FMT. 14–179 per group per analysis.	NA	At weaning: oral gavage, 100µL per mouse.	Breeding (ages 7–8w). Offspring were tested from 6w and followed until P45.	NA	Group 2 vs 3 MB, OFT, USV: more ASD-like behaviors. 3-CST: No differences. DSI: decreased. Enrichment for splicing of ASD-related genes in brain.	Group 2 vs 3 α-diversity: decreased. β-diversity: different.	NA
Qi Z et al, 2021, China <sup>60</sup>	3 groups of pregnant mice (ages 7w): 1. FMT from ASD children(10), 2. valproic acid(8), 3. normal(9).	NA	Rectal: 0.2mL/100g per 2d from 0.5d after conception to 21d after delivery.	Randomly male offspring (ages 4w)	NA	Group 1, 2 vs 3 Hypoevolutism, 3-CST, OFT: ASD-like behaviors.	Group 1, 2 vs 3 Abundance of <i>Lactobacillus</i> and <i>Collinsella</i> : increased.	NA
Xiao L et al, 2021, China <sup>61</sup>	2 groups of mice (ages 4w) with FMT from ASD and TD children: 1.ASD-FMT, 2.TD-FMT.	NA	Oral gavage, 200µL per mouse.	3w	NA	Group 1 vs 2 Olfactory habituation/dishabituation test: less sensitivity to social odors. OFT, 3-CST: more ASD-like behaviors.	Group 1 vs 2 α-diversity: no significant differences. β-diversity: different.	NA
Chen K et al, 2020, China <sup>62</sup>	A group of health mice and 3 groups of MIA-induced ASD mice (ages 3w): 1. cultured-FMT, 2. original-FMT, 3. saline.	NA	At weaning: oral gavage, 200µL/2d for 7 times per mouse.	5w	NA	Group 1, 2 vs 3 OFT, 3-CST, MB, self-grooming tests: improved.	Group 1, 2 vs 3 S24-7, <i>Clostridiaceae</i> , <i>Prevotella</i> _other, <i>Candidatus</i> <i>Arthromitus</i> : decreased. <i>Ruminococcaceae</i> , <i>Oscillospira</i> : increased	NA
Goo et al, 2020, Korea <sup>63</sup>	2 groups of Fmr1 KO mice (ages 8–17w): 1. FMT(9), 2. vehicle-treated(8).	NA	Oral 200µL/d for 4w.	4w, behavioral tests after 2w of FMT.	NA	EPM, OFT, Y-maze, NOR, SIT: memory deficits, social withdrawal improved.	The amount of <i>A. muciniphila</i> : increased.	NA
Abuaish et al, 2021, 2022, Saudi Arabia <sup>64,65</sup>	A group with saline +3 groups of propionic acid rat model of ASD (ages 4w): 1. FMT, 2. BF, 3. saline. 7 per group.	NA	FMT: oral gavage, 1g/kg per mouse. BF: longum BB536, 1 × 10 <sup>9</sup> CFU/d for 22d.	5w	NA	Group 1, 2 vs 3 3-CST: improved.	Group 1, 2 vs 3 fecal clostridium spp. balance: restored, BDNF expression: normalized. GST levels: increased.	NA

**Abbreviations:** Ref, reference; NA, not available; TD, typically-developing; MB, marble burying; OFT, open field testing; USV, Ultrasonic vocalization; 3-CST, three-chamber sociability test; DSI, direct social interaction; BF, bifidobacterium; MIA, maternal immune activation.

In an animal experiment, fecal samples from ASD and control children were transplanted into germ-free mice. ASD and control transplanted mice showed different behavioral characteristics of ASD and significant differences in gut microbiota. Metabolomics analysis showed that the changes of amino acid and 5-hydroxytryptamine (5-HT) metabolic pathways were significant in serum metabolomics of both children and mice with ASD after transplantation. ASD mice showed lower expression of 5-HT reabsorption transporter and serotonin 1A receptor proteins, and higher expression of tryptophan hydroxylase 1 protein in the colon.<sup>61</sup>

A study showed that FMT from healthy human gut microbiota significantly improved anxiety-like and repetitive behaviors and increased serum chemokine levels in ASD mice, including GRO- $\alpha$  (CXCL1), MRIP-1  $\alpha$  (CCL3), MCP-3 (CCL7), RANTES (CCL5) and Eotaxin (CCL11), which are involved in neural development and synaptic transmission of the central nervous system.<sup>62</sup> Another study found that FMT from naive wild-type mice improved memory deficits and social withdrawal of the *Fmr1* knock out mice, with normalizing the content of *A. muciniphila* to wild-type level and decreasing the levels of TNF $\alpha$  and Iba1 in their brains.<sup>63</sup> Moreover, studies have shown that FMT therapy repair the social interaction of the ASD mouse models induced by propionic acid. FMT treatments significantly increased the abundance of *Clostridium*, *Bifidobacterium*, *Marvinbryantia* and *Butyricoccus*, and were negatively correlated with succinic acid synthesis, pyruvate metabolism, nitrogen metabolism,  $\beta$ -lactam resistance and peptidoglycan synthesis. Propionic acid significantly increased the abundance of fecal *C. perfringens*, decreased the content of *Clostridium* cluster IV and increased the expression level of BDNF in the hippocampus. FMT treatment could restore fecal *Clostridium* spp. balance, normalize BDNF expression and increase GST levels.<sup>64,65</sup>

It was reported that the addition of p-cresol to drinking water induced social deficits and repetitive behaviors in ASD mice. P-cresol-treated mice exhibited more frequent head shakes and circling events, but similar hyperactivity and anxiety compared with normal mice, indicating that p-cresol selectively induced ASD core symptoms. Transplanting the fecal microbiota of p-cresol treated mice to normal mice induces typical ASD behavior and increases p-cresol production. However, transplantation of fecal microbiota from normal mice to p-cresol treated mice could restore their social behavior, VTA dopamine neuronal excitability and fecal p-cresol levels.<sup>66</sup> On the whole, social behavioral abnormalities in ASD mice can be corrected by the administration of FMT.

## Effects of FMT on ASD

### Effect of FMT on Gastrointestinal and Neurobehavioral Outcomes

FMT studies in ASD patients were summarized (Table 3). A small open-label clinical trial was conducted in 18 children diagnosed with ASD. FMT was performed after 2 weeks of antibiotic treatment and intestinal clearance. The Gastrointestinal Symptom Rating Scale (GSRS) showed about 80% improvement in gastrointestinal symptoms. Behavioral symptoms of ASD also improved significantly, and continued to improve after 8 weeks of treatment. Sequencing analysis showed that part of the donor microbiota was successfully transplanted, the intestinal environment was improved, the total bacterial diversity and the abundance of *Bifidobacteria*, *Prevotella* and *Deiphosphococcus* were increased, and remained unchanged after 8 weeks.<sup>67</sup> 8 autistic children showed improvement in gastrointestinal symptoms and a greater degree of improvement in ASD symptoms after 2 years of FMT treatment. Significant changes in the gut microbiota of children who received FMT persisted 2 years after treatment, including a significant increase in microbial diversity and an increase in the relative abundance of *Bifidobacteria* and *Prevotella*, suggesting the long-term safety and efficacy of FMT in improving ASD symptoms.<sup>68</sup>

In China, 16 children with typical development (TD) and 40 children with ASD were enrolled for 12 weeks. Children with ASD were treated with FMT for 4 weeks and followed up for 8 weeks. At the first week, there were significant differences in behavior, gastrointestinal symptoms and microbiota between children with ASD and TD. FMT could improve gastrointestinal and ASD symptoms and serum neurotransmitter levels. Both oral and rectal FMT improved gastrointestinal symptoms, and there was no significant difference between the two approaches. FMT can promote the colonization of donor microbiota and transfer the bacterial community of children with ASD to TD or donor children. The abundance of *Eubacterium coprostanoligenes* was positively correlated with high GSRS score, while FMT reduced

**Table 3** FMT Studies in ASD Patients

Ref.	Design	Pre-FMT	FMT	Follow-Up	GI Outcomes	Neurobehavioral Outcomes	Microbiota Changes	Adverse Effects
Kang DW et al, 2017, USA <sup>67</sup>	Open-label, FMT:18 ASD children (ages 7–16y) with moderate to severe GI symptoms. No FMT:20 age-and-gender-matched typically developing children without GI symptoms.	Oral vancomycin and acid pump inhibitor, bowel cleansing	Randomly, 12 oral (SHGM): $2.5 \times 10^{12}$ cells/d for 2d, then $2.5 \times 10^9$ cells/d for 8w.6 rectal (enema):single rectal dose of $2.5 \times 10^{12}$ cells, after 1w, $2.5 \times 10^9$ cells/d orally for 7w.	8w.	GSRS:77% reduction. DSR: improved.	CARS:24% reduction. PGI-III, ABC, SRS, VABS-II: improved.	$\alpha$ -diversity: increased. $\beta$ -diversity: changed toward donor. Abundances of <i>Bifidobacterium</i> , <i>Prevotella</i> and <i>Desulfovibrio</i> increased.	Vancomycin:28–39% mild to moderate hyperactivity, tantrums or aggression. Oral SHGM: 5% nausea.
Kang DW et al, 2019, USA <sup>68</sup>	Open-label, FMT:18 ASD children (ages 7–16y) with moderate to severe GI symptoms. No FMT:20 age-and-gender-matched typically developing children without GI symptoms.	Oral vancomycin and acid pump inhibitor, bowel cleansing	Randomly, 12 oral (SHGM): $2.5 \times 10^{12}$ cells/d for 2d, then $2.5 \times 10^9$ cells/d for 8w.6 rectal (enema):single rectal dose of $2.5 \times 10^{12}$ cells, after 1w, $2.5 \times 10^9$ cells/d orally for 7w.	2y after FMT	GSRS:58% reduction. DSR: still improved	CARS:47% reduction. PGI-III, ABC, SRS, VABS-II: improved.	$\alpha$ -diversity: increased. $\beta$ -diversity: similar to pre-FMT. Abundances of <i>Bifidobacteria</i> and <i>Prevotella</i> still increased.	NA
Li N et al, 2021, China <sup>69</sup>	Open-label, FMT:40 ASD children (ages 3–17y) with GI symptoms. No FMT:16 age-and-gender-matched typically developing children without GI symptoms.	Bowel cleansing	27 oral (freeze-dried capsules): $2 \times 10^{14}$ CFU/w for 4w.13 rectal (colonoscopy): single rectal dose of $2 \times 10^{14}$ CFU/w for 4w.	8w	GSRS:35% reduction. DSR: improved.	CARS:16% reduction. ABC, SRS, SAS: improved.	$\alpha$ -diversity: no significant change. $\beta$ -diversity: changed toward donor. Abundance of <i>Eubacterium coprostanoligene</i> decreased.	Oral capsules:3.7% fever, hyperactivity, tantrums or aggression. Rectal:7.7% hyperactivity

**Abbreviations:** Ref, reference; GI, gastrointestinal; GSRS, Gastrointestinal Symptom Rating Scale; DSR, daily stool records; CARS, Childhood Autism Rating Scale; PGI-III, Parent Global Impressions III; ABC, Autism Behavior Checklist; SRS, Social Responsiveness Scale; VABS-II, Vineland Adaptive Behavior Scale II.

its abundance and might be associated with the improvement of ASD symptoms.<sup>69</sup> In addition, a multicentre, double-blind, randomised, placebo-controlled trial of FMT for ASD is ongoing in China currently.<sup>70</sup>

The fecal and plasma metabolites of 18 children with ASD and 20 healthy children were compared. Among the 619 plasma metabolites detected in children with ASD, the levels of niacinamide nucleoside and other metabolites decreased, while the levels of octanoate and heptanoate increased. Among the 699 fecal metabolites detected, there was no significant difference between the two groups, but the level of p-cresol sulfate was not significantly increased in the children with ASD. After FMT, the plasma metabolic profile of children with ASD changed significantly, including nicotinate/nicotinate and purine-related metabolites, and the reduction of fecal sulfate level of p-cresol was similar to that of healthy children.<sup>71</sup>

FMT is a novel method in the treatment of children with ASD, which can relieve not only gastrointestinal symptoms, but also neurobehavioral symptoms.<sup>72</sup> However, as data on the long-term effects of this treatment is still limited, further research is needed, but it can be expected, based on contemporary scientific evidence and experimental studies, that FMT will be formally applied in the treatment of ASD in the future. Unresolved questions include which microbiome in the gut is beneficial and which is harmful, how to safely and effectively implant beneficial bacteria into the body, and how to extract and eliminate harmful microbes before transplantation.<sup>73</sup> In future studies, large-sample randomized controlled clinical studies are needed to determine the mechanism of FMT in the treatment of ASD and the optimal method of FMT.

## Risk of Adverse Events

All adverse events of FMT were classified as short-term (48 hours after FMT) and long-term (3 months after FMT).<sup>74</sup> FMT is highly effective for treating recurrent *Clostridioides difficile* infection (RCDI). In a large single-center prospective study conducted in 609 adult patients with RCDI, more than 60% of the patients had diarrhea during short-term follow-up after FMT, but it lasted less than a week, and the long-term risk of adverse events and complications of infection is low.<sup>75</sup> A single-center retrospective study was performed to investigate the safety of FMT in children, the incidence of short-term adverse events was 26.32% (30/114), and the most common short-term adverse events were abdominal pain, diarrhea, fever and vomiting, all of which were self-limited and asymptomatic within 48 hours. In the study, no relevant long-term adverse events happened during 3-month follow-up, only one child with primary immunodeficiency died of sepsis and liver failure 4 weeks later after treatment with FMT for chronic intractable diarrhea.<sup>76</sup> An open-label study and two-year follow-up showed that FMT is relatively safe in significantly alleviating gastrointestinal and neurobehavioral symptoms in children with ASD, without any adverse negative side effects. In general, FMT appears safe both in the short-term and long-term.

## Conclusion

The microbiota-gut-brain axis plays an important role in the gastrointestinal symptoms and neurodevelopmental dysfunctions in ASD patients. FMT can alter the gut microbiota and improve the gastrointestinal as well as neurobehavioral symptoms in ASD patients, which is a promising treatment strategy. However, not only well designed human studies are needed to confirm the effect, but also elucidated research to explore the mechanism. Specific microbiota interventions need to be identified to further optimize treatment options.

## 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.

## Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.



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