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Research Progress on Gut Microorganisms Affecting Mental Illness and Cognitive Function

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Abstract:

Gut microorganisms affect host's depression, anxiety and other mental diseases. Recent studies have shown that there is a certain correlation between gut microorganisms and diseases of the central nervous system. On the one hand, gut microorganisms can affect the development and function of the brain through the gut brain axis. On the other hand, the brain also changes the structure and composition of gut microbes through the gut brain axis. This paper reviews the interaction between gut microorganisms and brain through the gut brain axis, focusing on the study of gut microorganisms and brain function, psychology, cognition and other fields. It provides a new idea for the research of related mental diseases and cognitive dysfunction.

Keywords*: Gut microbiota; Gut brain axis; Mental illness; Cognitive function.*

I. INTRODUCTION

About 100 trillion microorganisms are colonized in the hidden and mysterious kingdom of gut, which is 10 times the number of human cells. The genes encoded by the gut flora are 150 times the genes encoded by the host cells. Where, many gene expression products are correlated with the metabolism and health of the host [1]. All symbiotic microorganisms have a lifelong symbiotic relationship with their host. Unicelluar life is present throughout evolutionary history of multicelluar life. Humans and other hominids have evolved alongside with their gut bacteria for at least 15 million years. Such close bacteria-host interaction suggests that many biological and psychological characteristics of the host may be input through the symbiotic relationship with the symbiotic bacteria [2].

In the past decade, research on gut microorganism has not only opened a new chapter for the study of various physiological diseases, but also brought revolutionary breakthroughs to the study of psychological and mental illness. Psychological and mental illnesses are related to not only the brain, but also the gut brain and gut microorganisms. Studies have found that during the treatment of these diseases, changes in diet and regulation of intestinal flora can help relieve symptoms [3]. Gut microorganisms and the brain communicate with each other through a variety of pathways, including the immune system, tryptophan metabolism, the vagus nerve, and the enteric nervous system. Numerous recent studies have shown that gut microorganisms are closely associated with a variety of mental illnesses, including autism, depression, anxiety, schizophrenia, Parkinson's disease, and Alzheimer's disease [3,4,5]. In addition to alleviating mental illness, probiotic intake may hinder diet-induced obesity, regulate cardiovascular function and blood pressure, and possibly even serve as an adjunctive treatment for cancer [6,7]. The use of probiotics and prebiotics has a certain alleviation

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effect in disease treatment, but with varying results. Further human research is needed, including analysis of flora composition in specific patient groups, as well as intervention effects of probiotics, prebiotics, flora transplantation and diet [8].

This study mainly reviews the effect of gut microorganisms on mental illness, illustrates the gut microorganisms and gut brain axis from the basis and pathway of gut brain axis. It discusses the pathways and mechanisms through which gut microorganisms affect the brain, thus affecting mental illness and cognitive function. The study provides clinical reference for treating mental illness by gut flora adjustment, also providing reference for regulating gut flora to alleviate diseases by probiotics administration, fecal bacteria transplantation, etc.

II. GUT MICROORGANISM AND GUT BRAIN AXIS

The brain is an important guarantee for controlling and regulating the life activities of the body and various basic neurological functions such as breathing and digestion. Gut microorganisms are called the "second brain", which maintain a long-term and stable symbiotic relationship with the body [9]. The gut brain axis belongs to a bidirectional response system. Mediated by immune, neuroendocrine and vagus nerves, it connects brain cognition with peripheral gut function [10]. Relevant literature [11-13] points out that there is a close connection between the gut microorganism and brain axis, the gut microorganisms bidirectionally interact with the brain through the gut brain axis pathway, which directly interact with a variety of elements such as inter-brain nerves, hormones, immunological signals, etc. thus playing a role in regulating brain development and related functions. Hence, the relationship between gut microorganisms and brain development, brain function has become a research focus.

2.1 Gut Brain Axis Basis

The body has an intimate, stable and lifelong interdependent relationship with bacteria, viruses, fungi, protozoa and other microbial species. Microorganisms can be colonized on all surfaces of the body, but the largest microbial population is stored in the gut. Generally, the stable physiological functions of the host are maintained by beneficial microorganisms. If the gut microorganisms are disturbed in the early stage, the digestive, metabolic and immune functions of the body will be impaired, resulting in abnormal neurodevelopment [14]. The establishment of neonatal gut microorganisms is influenced by the microbial population of the mother's birth canal and is established through maternal vertical transmission. The gut brain axis plays a role in the coordination of host nervous system structures such as the central nervous system, hypothalamic-pituitary-adrenal axis, enteric nervous system. It is through this pathway that gut microorganisms affect the brain [15]. The gut brain axis provides an important network for gut microorganisms, gut and brain functions, directly affects the developmental functions of gut and brain, while the brain plays a role in regulating gut microorganism function and community structure [16].

The current study on the role of gut microorganisms and gut brain axis depends on two approaches: (1) germ-free mice. By transplanting bacteria from germ-free mice, observe the effect of normal gut microorganisms on the function of the gut-brain axis, or the effect of certain bacteria and viruses on the gut brain axis. Shuang Zheng et al. [17] colonized the gut microorganism of allergic mice and non-allergic mice in germ-free mice gut. Through comparison between allergic mice and non-allergic mice, it was found that, compared with the non-allergic mice, the jejunal villus epithelial cells of the allergic mice displayed focal necrosis and shedding, as well as significantly more serious inflammatory cell infiltration. Or, control

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experiments can be carried out using mice without special pathogens to observe the effects of different external environmental factors on the physiological functions and behavioural performance of the two experimental animals. (2) Germ-free mouse replacement and supplementation. Antibiotics were supplemented to germ-free mice to affect the normal microbial flora structure of mice, observe the mice symptoms before and after supplementation, and then detect the connection between flora and gut brain axis. In study of Gaofeng Wu et al. [18], 128 healthy mice were selected and divided into blank control group, regulation group, prevention group and model group. Immune regulation and cytokine secretion in antibiotic-mediated mice were affected. Yuan Liu et al. [19] established a model of gut flora imbalance in early life mice, and randomly divided 60 weaned mice into high-dose antibiotic group, low-dose antibiotic group and control group. It was found that high-dose and low-dose antibiotic group had lower body weight than the control group, the high and low dose groups had decreased diversity and richness in fecal flora, with the dominant gut flora changed.

2.2 The Gut Brain Axis Pathway

The gut brain axis refers to a two-way signal communication network between the mammalian brain and the gastrointestinal tract, which connects the brain and the gut brain through neural, hypothalamic-pituitary-adrenal (HPA) axis and immune pathways. With the in-depth study of gut microorganisms, researchers have realized that the functions of individual systems such as metabolism, immunity, endocrine, and nerves are all related to the gut brain axis, and gut brain changes (such as abnormal gut microorganisms) will affect the brain and behaviour, while brain changes will also affect gut brain function and structure. It is a new direction for future neuroscience development to combine gut brain and brain. Focusing on gut microorganisms in treatment of mental and neurological diseases may be a new trend in the future neuroscience development [20 -25].

The three pathways of immunity, neuroendocrine and vagus nerve affect the bidirectional regulation of gut flora and brain. The immune cells contained in intestinal lymphoid tissue account for 70%~80% of the total body, which are divided into commensal bacteria and pathogenic bacteria. Changes in gut flora affect the intestinal immune system [26]. Xingyin Liu et al. [27] found that mutation of demethylase (KDM5) in the Drosophila gut flora plays an important role in mediating related social behaviour abnormalities. Using multiple KDM5-deficient Drosophila models, this study revealed that KDM5 modulates Drosophila social behaviour through the gut brain axis by regulating innate immune pathways, thus affecting gut barrier and flora composition. Patients with neurological diseases are often accompanied by complications of the intestinal system. For example, Wentao Fan et al. [28] reported that the stool samples of 32 patients with post-stroke depression were qualitatively analyzed using the Roche/45 high-throughput sequencing platform. Compared with the normal group, the post-stroke depression group had increased bacterial species OTU information content and diversity index in bacterial flora, displaying statistical significance. The gut endocrine system is the largest endocrine organ in the body that affects the central nervous system activity of the brain. The hypothalamic-pituitary-adrenal axis is an important part of endocrine transmission, which regulates the structural diversity and distribution of gut flora through the release of cortisol.

III. THE IMPACT OF GUT MICROORGANISMS ON BRAIN DEVELOPMENT AND FUNCTION

3.1 The Impact of Gut Microorganisms on Brain Development

Gut microorganisms influence brain development and function. Research has found that young mice

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raised in sterile environments are more prone to anxiety and have certain cognitive defects. A study by Desbonnet et al. [29] evaluated the effects of reduced gut microorganisms in mice on cognition, mood, and behaviour in adulthood. In the experiment, the weaned mice were given drinking water containing mixed antibiotics. It was found that mice given with antibiotics had decreased number of microorganisms in the cecum, with the structure changed. Behavioural test results found that the mice were less anxious, with cognitive disorder shown. The interaction between the gut microorganism and the host is an important window that affects neurodevelopment. If gut flora is disturbed in the early life (an important window), it will affect the information exchange of the gut brain axis, lead to corresponding changes in normal developmental trajectory of the brain and increase the susceptibility to neurological diseases in the future [30]. Some studies [31] pointed out that the mental behaviour of neonatal mice is due to the exposure of normal neonatal animals to maternal vaginal flora, which promotes the colonization of gut flora and strengthens the immune system development in the host. However, some studies [29] believe that in the natural state, the different mental behaviours of newborn mice are mainly because the normal newborn animals will be exposed to the maternal vaginal flora during the production process, which boosts colonization of gut flora and development of the host immune system in the later stage. Dominguez-Bello et al. [32] showed that changes in the maternal flora during pregnancy can indirectly affect the fetus, the original maternal flora can be vertically transmitted to the next generation during childbirth, and the flora derived from breast milk can direct the flora establishment and immunity development of neonates, etc.

3.2 The Impact of Gut Microorganisms on Brain Function

The functional areas of the brain include hypothalamus, pituitary, basal ganglia, limbic system, etc., and different functional areas affect different physiological functions of the body. Normally, gut microorganisms will affect the levels of 5-HT neurotransmitters, dopaminergic neurotransmitters and other neurotransmitters, which directly act on various functional areas of the brain, resulting in behavioural changes [33]. At the same time, gut microorganisms can affect brain learning function and memory function. Lu Yang [34] investigated the effect of fecal bacteria transplantation on Alzheimer's disease mice, analyzed the differences in gut microorganisms between normal mice and Alzheimer's disease mice, and tested whether fecal bacteria transplantation can alleviate pathological characteristics of Alzheimer's disease mice. It was found that probiotics and prebiotics can effectively regulate neurological diseases and improve the therapeutic effect; the Alzheimer's disease mice had decreased diversity and species abundance in gut microorganisms; fecal bacteria transplantation made species abundance of gut microorganisms in Alzheimer's disease mice approach the healthy group, which improved the cognitive function of mice in terms of behaviour, improved the ability to resist oxidative damage, reduced the level of inflammatory response, promoted the development, survival of neurons, reduced Aβ amyloid deposition, and alleviated the pathological features of Alzheimer's disease.

IV. GUT MICROORGANISMS AND RELATED MENTAL ILLNESSES

4.1 Autism Spectrum Disorder

Autism spectrum disorder, also known as autism, is a serious neurodevelopmental disorder with unclear pathogenesis. Gut brain development is synchronized with brain development, so abnormal development of gut microorganisms during a critical period of infant development may increase the risk of autism. Gut microorganisms can affect autism through metabolite, immune, neuroendocrine, and vagus nerve. Specific

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beneficial microbial strains can alleviate and treat autism mainly through the microorganism-gut-brain axis by regulating microecological balance and anti-infection, regulating host metabolism and absorption, and reducing gut leakage [35]. Autism is a complex disorder, and gastrointestinal diseases are often found in autism spectrum disorder (ASD) patients, but the pathophysiological mechanisms remain unclear [36]. The insufficient understanding of the pathophysiological mechanisms of the gut brain axis in autism patients hinders the development of precision microbial therapy for ASD [37]. Children with autism spectrum disorder (ASD) are four times more likely to develop gastrointestinal disorders than children without ASD. Since there is evidence of high correlation between gastrointestinal diseases and ASD, probiotic therapy has been proposed as a treatment for ASD children with severe gastrointestinal symptoms [38]. Shindler A E et al. investigated genetic biomarkers of gastrointestinal dysfunction symptoms to further understand the genetic risk of gastrointestinal dysfunction associated with autism [39]. Autism is associated with gastroenterological and immunological disorders as well as changes in gut microorganism content. Gut microorganism distribution in autistic patients and autistic rodents differ from typical controls. The discovery of this difference makes researchers hypothesize a functional link between gut bacteria and autism [40]. Human studies reveal some bacterial differences between autistic and non-autistic individuals. At the same time, great differences exist in the identification of bacterial markers of autism, and the proportion of bacteriophyta is inconsistent or even contradictory in different studies [41]. In another study, feeding pregnant mice with high-fat diet induced some features of autism in offspring [42]. In addition to the behavioural and microorganism abnormalities associated with autism, the researchers found that autistic mice developed chronically enhanced deficits in the ventral tegmental area after social activity, with number of hypothalamic oxytocin immune response neurons decreased. Furthermore, microorganisms transplanted from offspring of mice fed with a high-fat diet to normal mice elicited a similar tendency in recipients, which provides further evidence for the causal effect of gut bacteria in the development of autism phenotypes. Treatment with probiotics reduces these behavioural and neurological abnormalities.

Zhou Ziyun[43] studied dietary behaviour and gut microorganisms in children with autism spectrum disorder, selected children with autism spectrum disorder as the experimental group, with normal children in the control group. The experimental group displayed symptoms such as dysphagia, drooling, chewing difficulty, nausea and retching. 67% of the experimental group children could not eat independently, 13% of the children refused everything and refused to try new things, and dietary behaviour problems were closely related to the diversity and abundance of gut microorganisms. Yan Cong et al. [44] studied the gastrointestinal problems of autism spectrum disorder children, finding that autism spectrum disorder children with gastrointestinal problems are prone to behavioural problems. Sharon G found that after transplanting fecal bacteria from autism children to germ-free mice through fecal flora transplantation, the offspring of flora recipient mice also developed autism-like symptoms (including behaviour, flora, transcriptome and metabolome). Moreover, supplementation of key metabolites lacking in ASD offspring mice can significantly reduce autism symptoms in autism model mice [45].

4.2 Depression

Depression is a common mental illness in modern society. Modern biology believes that depression is not only a mental illness, but also a physical illness. However, mental illness and physical illness are closely related. Patients with mental illness are often accompanied by physical illnesses such as gastrointestinal disorders including constipation, diarrhea, and stomach bloating. These symptoms are often ignored by

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psychiatrists. In addition to gastrointestinal diseases, the incidence of mental diseases (such as depression and anxiety) is also significantly increased in patients with other chronic diseases (metabolic diseases such as diabetes, allergic diseases, autoimmune diseases, etc.). The latest scientific evidence shows that mental illness may be sourced from gut microorganisms, and most mental illnesses may be gastrointestinal diseases in nature. Focusing on gut microorganisms in treatment of mental illness may be a new trend in the future psychiatric development [46]. In 2017, Bambling et al. [47] conducted a pilot experiment, in which 12 patients with refractory depression were treated with probiotics and magnesium orotate at the same time. After 8 weeks, the depression was significantly reduced in the patients, so conventional treatment was given, but retesting after 16 weeks found that the patient's symptoms recurred. These two studies suggest that attention to improving the gut microorganism during conventional antidepressant treatment may yield better results. Both clinical studies and animal experiments have found that supplementation with psychobiotics can reduce depression symptoms and even achieve similar effects as traditional treatments. In a randomized controlled placebo study in depressed patients, supplementation with psychobiotics could reduce depressive, anxiety symptoms and alleviate cognitive and metabolic abnormalities in patients [48]. Songze Li et al.[49] investigated the correlation between depressive symptoms and gut microorganisms in breast cancer patients. Twenty-eight breast cancer patients with depression were selected as the depression group, and 28 breast cancer patients without depression were selected as the control group. The study found that depressive symptoms in breast cancer patients were correlated with Bacteroidetes, Lactobacillus and Klebsiella in the gut flora. In addition, the brain, endocrine, immune, and gut brain functions of depressed patients were abnormal, and the abnormal function of the gut brain axis may be the main pathological mechanism of depression.

Changes in gut flora affect gut brain axis function, which may promote the occurrence of depression. By reconstructing the balance of gut flora in patients through probiotics, prebiotics, healthy diet, and fecal flora transplantation, it is possible to alleviate or even treat depression. It has become a hot topic in neuroscience and psychology to change mental diseases such as depression and anxiety by regulating the patients' gut microorganisms, and how to maintain good gut flora may be the future direction for the prevention and treatment of depression. Studies have shown [50,51] that gut flora was significantly changed in depressed patients. Some studies suggest that, in general, the flora diversity and richness were decreased in depressed patients. Compared with healthy individuals, at the phylum level, Bacteroidetes and Proteobacteria contents were increased in the feces of depressed patients, while levels of Firmicutes were decreased; at the family level, the content of Prevotella was increased; at the genus level, the content of Prevotella increased, while the content of Faecalibacterium and Ruminococcus decreased; the contents of Bifidobacterium and Lactobacillus decreased in varying degrees [52]. Although these studies have found that fecal flora was different between depressed patients and healthy individuals, the specific differences are still controversial [53,54], which may be related to the use of different diagnostic criteria, inclusion criteria and fecal flora detection methods by researchers. A recent large-scale study of the Flemish Gut Flora project also found differences in the distribution of gut microorganism among depressed people. After the confounding effect of antidepressants was taken into consideration, this difference still existed [55]. Coprococcus and Dialister species are absent in depressed populations, while their presence in nondepressed populations is positively associated with quality of life scores [55], though the latter does not suggest depression [56].

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4.3 Schizophrenia

Schizophrenia is a complex multifactorial mental illness, with obstacles in perception, emotion, thinking, and behaviour. The course of disease migrates slowly, often developing into mental activity decline. The gut brain axis is an information exchange system between the gut and the brain, which is composed of immune, vagus, and neuroendocrine pathways. The gut flora affects the brain and behaviour through the gut brain axis. Often accompanied by gastrointestinal inflammation and flora imbalance, schizophrenia may be alleviated by adjusting gut and flora balance with probiotics. Evidence suggests that the presence of Candida albicans is associated with poor psychiatric symptoms in male schizophrenic [57]. A recent study describes specific taxa associated with severity of schizophrenia, including the family Acrosorium polyneurm Okam and Lagerheimia. Moreover, in addition to altering glutamic acid signaling, FMT from these schizophrenic to germ-free mice also causes schizophrenic phenotype in animals [58].

Increasingly more evidence suggests that the gut microorganisms play a role in the pathogenesis of schizophrenia through the gut-organ-brain axis. After transplanting the fecal flora from schizophrenic into antibiotic-treated mice, behavioural abnormalities such as psychomotor hyperactivity and impaired learning and memory occurred in the recipient animals. At the same time, the mice had decreased level of tryptophan, the kynurenine-kynurenic acid pathway for the catabolism of tryptophan in the brain and blood had increased activity, with neurotransmitters dopamine and serotonin increased in specific regions of the brain [59].

4.4 Other Mental Illnesses

Alzheimer's disease is a chronic aging disease characterized by cognitive decline, which is the most common form of dementia. Patients often show progressive cognitive impairment and changes in personality and behaviour. It is generally believed that the pathogenesis of Alzheimer's disease is the result of the interaction between genetic factors and environmental factors. However, recent studies have shown a significant correlation between changes in gut flora and cognitive behaviour. By adjusting gut flora through probiotics, antibiotics, and fecal transplantation, it is possible to modulate host cognitive behaviour. Adjusting the gut flora balance through healthy diet or probiotic intervention may provide a new direction for the treatment of Alzheimer's disease. Studies found that, compared with cognitively normal elderly, different levels of secondary bile acids existed in the serum of patients with Alzheimer's disease and those with mild cognitive impairment, which is associated with brain pathology [60]. Furthermore, altered profile of gut organism is associated with cognitive impairment in healthy elderly [61].

Parkinson's disease is the second most common neurodegenerative disease after Alzheimer's disease, which is more prevalent in the elderly. The gut flora affects Parkinson's disease through the gut-brain axis, and altered profile of gut microorganism in the case of Parkinson's disease have been described in various studies [62,63]. In fact, FMT in Parkinson's disease patients and Parkinson's disease mouse models resulted in dyskinesia and neuroinflammation, further demonstrating the correlation between gut flora and Parkinson's disease [63]. Epidemiological studies suggest that patients undergoing complete trunk vagotomy in peptic ulcer treatment face a reduced risk of Parkinson's disease with age, which provides some possible evidence for the possibly involved microorganism-organ-brain signaling [64,65]. A recent meta-analysis identified a clear benefit of Helicobacter pylori eradication in improving Parkinson's disease symptoms [66].

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V. GUT MICROORGANISM AFFECTS COGNITIVE FUNCTION

The third part of the paper reviews the impact of gut microorganisms on cognitive function in Alzheimer's patients. This part mainly reviews the impact of gut microorganisms on cognitive function. Studies in rodents have found that gut flora has a significant effect on cognitive processes [67]. A classic animal experiment by Weill Cornell Medicine examined the impact of microbial population on the brain's ability to learn. Researchers [68] let the mice learn the elimination of fear memory. Specifically, the mice were trained to form a conditioned reflex by linking a sound with a slight electric shock, so that the mice froze in fear after hearing the sound. Then, when the shocks no longer appeared at the same time as the sound, the mice slowly removed their fear of the sound under normal circumstances. However, after antibiotics were given to adult mice, as the flora was eliminated, the mice still exhibited fear response to the voice prompt. A similar situation occurred in another group of mice grown in a sterile environment and lacking microbial population, and previous fear associated with the sound was difficult to dispel. This suggests that changes in gut flora can alter the function and structure of brain neurons, thereby affecting cognitive function and behaviour in animals. Compared with germ-free mice, mice given probiotics performed better in learning and memory in a series of cognitive tasks designed to test learning and memory [69]. Antibiotic-treated mice exhibited poorer spatial memory and higher anxiety levels, which were somewhat alleviated by administration of probiotics [70].

Gut microorganisms may also influence executive function supported by the prefrontal cortex. Mice supplemented with prebiotics for 3 weeks displayed greater cognitive flexibility compared to controls [71]. At the same time, this study also found that short-chain fatty acid (SCFA) acetates (probiotic metabolites) may mediate the observed behavioural and neurophysiological effects [71]. A recent study in healthy mice examined the interaction between probiotic administration and intake of unhealthy, energy-rich Western-style diet [72]. Mice fed with the diet developed location memory deficits, a diet-induced effect that was alleviated by supplementation with probiotics. Probiotics not necessarily positively affect host learning and memory. A recent longitudinal study of 1-year-old infants found that gut bacterial diversity was associated with visual reception and language acquisition at the age of 2 [73]. Interestingly, under lower gut bacterial diversity, cognitive performance was stronger. Nonetheless, this finding emphasizes the potential link between the microbial population and human cognitive development, which is certainly worthy of further study.

Our study regarding the impact of gut microorganisms on cognitive function has not reached inconclusive results in both animals and humans, and there are multiple differences. The main reason may be related to the different strains used or the variation of strains, as well as individual differences of participants, etc. At the same time, due to differences in statistical levels, the conclusions are also greatly different. However, the study regarding the impact of gut microorganisms on host cognitive function is still an important research field worth of expectations. These studies will further broaden the research field of cognitive neuroscience.

VI. CONCLUSION AND EXPECTATION

With the deepening study on gut brain axis, there is more and more evidence for the mutual communication between gut microorganisms and the brain. We can treat diseases by regulating gut flora to provide more reference for clinical treatment. For example, by providing the host with probiotics to regulate the flora, it is possible to relieve symptoms; through fecal bacteria transplantation, the feces of healthy people

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can be extracted and placed into the patient's body to rebuild the healthy flora.

However, researchers still need to further investigate the action mechanism of gut microorganisms in brain development and brain function, identify the molecular mechanisms by which gut microorganisms act on neuroendocrine, immune and microbial metabolic pathways, thus providing references for clinical treatment. It is foreseeable that gut microorganisms will play an increasingly important role in the treatment of brain diseases and related mental illness, which will also provide more and more assistance to the development of cognitive neuroscience.

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