Associations between Gut Microbiota, Brain Imaging, and Clinical Manifestations in Schizophrenia

Authors: Zhou Zhenyou, Kong Li, Chen Chuqiao, Kong Li, Chen Chuqiao

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Abstract

The microbiota-gut-brain axis hypothesis in the pathogenesis of schizophrenia has attracted increasing attention. Previous studies have preliminarily examined the association between gut microbial composition and brain imaging and clinical manifestations in patients with schizophrenia, but the specific pathways of action remain unclear. The current study summarizes the latest research progress and proposes a mechanistic hypothesis regarding how gut microbiota influences brain structure and function in patients with schizophrenia. The relevant content provides a theoretical foundation for further elucidating the pathological mechanisms of schizophrenia and for incorporating gut microbiota into the assessment and intervention of schizophrenia.

Full Text

The Relationship Between Gut Microbiota and Brain Imaging and Clinical Manifestations in Schizophrenia

Chen Chuqiao
Department of Psychology, Shanghai Normal University, Shanghai 200234, China
Shanghai Key Lab for Urban Ecological Processes and Eco-restoration, East China Normal University, Shanghai 200241, China
Neuropsychology and Applied Cognitive Neuroscience Laboratory, CAS Key Laboratory of Mental Health, Institute of Psychology, Chinese Academy of Sciences, Beijing 100101, China

Abstract
The microbiota-gut-brain axis hypothesis has garnered increasing attention in research on the pathogenesis of schizophrenia. Previous studies have preliminarily examined the relationship between gut microbiota composition and brain

imaging as well as clinical manifestations in schizophrenia patients, though the specific pathways remain unclear. This review summarizes recent research advances and proposes a mechanistic hypothesis regarding how gut microbiota influences brain structure and function in schizophrenia. These findings provide a theoretical foundation for further elucidating the pathological mechanisms of schizophrenia and for incorporating gut microbiota into the assessment and intervention of this disorder.

Keywords: schizophrenia, gut microbiota, microbiota-gut-brain axis, brain imaging, clinical manifestation

1. Introduction

Schizophrenia represents a group of severe mental disorders with unclear etiology, chronic course, and poor prognosis (Insel, 2010). The pathogenesis of schizophrenia remains incompletely understood, with widely recognized hypotheses including the dopamine hypothesis, serotonin hypothesis, and microbiota-gut-brain axis hypothesis (Nemani et al., 2015; Seeman, 2021; Stahl, 2018). Nemani et al. (2015) first proposed the microbiota-gut-brain axis hypothesis for schizophrenia, suggesting that bidirectional communication between gut microbiota and the central nervous system contributes to the pathological process of schizophrenia through the microbiota-gut-brain axis.

On one hand, gut microbiota can influence the brain through the intestinal immune system. Disruption of gut microbiota increases intestinal permeability, leading to translocation of harmful microbes and their products to other body sites and triggering inflammation, which subsequently increases blood-brain barrier (BBB) permeability. The homeostasis of neurotrophic factors produced by gut microbiota metabolism is disrupted, elevating the risk of brain inflammation and causing abnormalities in brain structure and function, such as damage to hippocampal neurons (Jiang et al., 2015; Kelly et al., 2005; Kelly et al., 2021; Ma et al., 2017). On the other hand, early-life colonization of gut microbiota affects central nervous system development. The establishment of gut microbiota communities occurs concurrently with neurodevelopment, with both processes sharing similar critical windows of vulnerability to insult (Heijtz et al., 2011). When the brain undergoes remodeling at the neuronal circuit and synaptic levels, gut microbiota influences and facilitates the refinement of neuronal circuits through its metabolites (Oliphant et al., 2021).

Previous research has identified significant differences in gut microbiota composition and diversity between schizophrenia patients and healthy individuals, typically characterized by reduced microbial diversity (Foster & Neufeld, 2013; Li et al., 2017; Vogt et al., 2017; Schwarz et al., 2018). Further studies have revealed associations between altered microbiota diversity and relative abundance in schizophrenia patients and structural and functional abnormalities in specific brain regions (Li et al., 2021; Ma et al., 2020; Wu, 2019). However, the specific relationship between gut microbiota alterations and brain structural and func-

tional impairments in schizophrenia remains unclear, as do the precise pathways through which gut microbiota influences brain structure and cognitive function via the microbiota-gut-brain axis. Therefore, this review examines research on abnormal gut microbiota structure in schizophrenia patients, summarizes current studies on the relationship between gut microbiota and brain structure and function, clarifies how gut microbiota may influence the pathophysiological processes of schizophrenia through the microbiota-gut-brain axis, and provides new insights into the pathophysiological mechanisms of schizophrenia.

2.1 Differences in Gut Microbiota Between Schizophrenia Patients and Healthy Individuals

The gut microbiota of healthy individuals is primarily composed of four phyla: Bacteroidetes, Firmicutes, Proteobacteria, and Actinobacteria, which account for 99% of total gut microbes (Lloyd-Price et al., 2016; Zhang et al., 2015; Zou et al., 2019). We conducted a comprehensive literature search of studies comparing gut microbiota differences between schizophrenia patients and healthy controls. In Chinese databases (CNKI, Wanfang, VIP), we searched using combinations of keywords including "schizophrenia,""mental illness"with "gut microbiome"and "gut microbiota."In international databases (Web of Science, PubMed, Cochrane Library, Science Direct), we used combinations of "schizophrenia," "psychiatry" with "gut microbiome," "gut microbiota," "gastrointestinal microbiome," and "gastrointestinal microbiota." We searched titles, keywords, and abstracts with a cutoff date of December 2021. Seven studies using 16S rRNA technology for gut microbiota gene sequencing in schizophrenia patients were included, four with Chinese participants and three with foreign participants (Table 1). Results indicated that differences between schizophrenia patients and healthy individuals primarily manifest in microbial diversity and relative abundance.

Table 1. Summary of Studies on Gut Microbiota Composition Differences Between Schizophrenia Patients and Healthy Controls

Study	SCZ/HC Group	Increased	Decreased	Notes
Shen et al., 2018	64/53	**Phylum:** Proteobacteria**Genus:** Succinivibrio, Megasphaera, Collinsella, Clostridium, Klebsiella, Methanobrevibacter	**Genus:** Blautia, Coprococcus, Roseburia	

Study	SCZ/HC Group	Increased	Decreased	Notes
Schwarz et al., 2018	28/16	**Family:** Lactobacillaceae, Halothiobacillaceae, Brucellaceae, Micrococcaceae**Genus:** Lactobacillus, Tropheryma, Halothiobacillus, Saccharophagus, Ochrobactrum, Deferribacter, Halorubrum	**Family:** Veillonellaceae**Genus:** Anabaena, Nitrosospira, Gallionella	
Nguyen et al., 2019	25/25	**Genus:** Anaerococcus	**Phylum:** Proteobacteria**Genus:** Haemophilus, Sutterella, Clostridium	No significant difference in α diversity between groups
Xu et al., 2020	84/84	**Phylum:** Actinobacteria**Order:** Actinomycetales, Sphingomonadales**Family:** Sphingomonadaceae**Genus:** Eggerthella, Megasphaera, Adlercreutzia, Bifidobacterium adolescentis, Clostridium perfringens	**Order:** Erythrobacterales**Family:** Alcaligenaceae, Enterococcaceae, Leuconostocaceae, Erythrobacteraceae**Genus:**	Significantly lower microbiota diversity in SCZ group

Study	SCZ/HC Group	Increased	Decreased	Notes
Li et al., 2020	82/80	**Phylum:** Actinobacteria**Genus:** Collinsella, Lactobacillus, Succinibacterium, Morgana, Corynebacterium, undefined Lactococcus, undefined Eubacterium	**Phylum:** Firmicutes**Genus:** Adlercreutzia, Anaerostipes, Lactococcus, Streptococcus faecalis	No significant α diversity difference; β diversity showed significant community-level separation
Manchia et al., 2021	38/20	**Absent in SCZ:Phylum:** Cyanobacteria**Family:** Pasteurellaceae, Cytophagaceae, Morganellaceae**Genus:** Acetobacter, Haemophilus, Turicibacter, Obesumbacterium**Species:** Streptococcus equinus, Coprococcus species, Streptococcus sanguinis		Significantly lower Shannon index for α diversity in SCZ group

Study	SCZ/HC Group	Increased	Decreased	Notes
Zhao et al., 2019	16/18	**Phylum:** Actinobacteria**Genus:** Bifidobacterium, Prevotella, Megamonas	**Phylum:** Bacteroidetes, Tenericutes**Genus:** Bacteroides, Faecalibacterium	Ace, Chao, and Shannon indices significantly lower; Simpson index significantly higher in patient group

Note: SCZ, schizophrenia; HC, healthy control; α diversity, microbial diversity within a single sample; β diversity, differences in microbiota composition between samples; Ace index, assesses species richness and evenness; Chao index, estimates OTU numbers.

2.1.1 Diversity Differences

Research findings consistently demonstrate that gut microbiota diversity is significantly lower in schizophrenia patients compared to healthy individuals. Xu et al. (2020) found that schizophrenia patients exhibited significantly reduced gut microbiota diversity compared to healthy controls, specifically showing decreased β diversity indices. This reduction in microbiota diversity could distinguish schizophrenia patients from healthy participants. Furthermore, schizophrenia patients' gut microbiota dysbiosis index was positively correlated with gut microbiota-related intestinal immunoglobulin A (IgA) levels and negatively correlated with microbiota diversity. Li et al. (2020) investigated differences in gut microbiota diversity between schizophrenia patients and healthy controls, finding no significant difference in α diversity (within-sample microbial diversity), consistent with Nguyen et al. (2019). However, β diversity (between-sample composition differences) showed significant community-level separation between groups, with the schizophrenia group showing significant reduction. Zhao et al. (2019) similarly found statistically significant differences in gut microbiota composition diversity between schizophrenia patients and healthy controls, with α diversity Ace, Chao1, and Shannon indices significantly lower in the patient group, while the Simpson index was significantly higher. Manchia et al. (2021) also reported significantly lower α diversity indices in schizophrenia patients compared to healthy controls.

2.1.2 Relative Abundance Differences

Beyond diversity differences, schizophrenia patients also exhibit significant differences in the relative abundance of gut microbiota components compared to healthy individuals. Previous studies have found that these differences manifest at multiple taxonomic levels. At the phylum level, schizophrenia patients show significantly increased Actinobacteria and Proteobacteria, and decreased Bacteroidetes and Firmicutes (Li et al., 2020; Xu et al., 2020; Zhao et al., 2019), though Nguyen et al. (2019) found decreased Proteobacteria abundance in schizophrenia patients compared to controls. At the family level, Schwarz et al. (2018) found significantly increased Lactobacillaceae, Halothiobacillaceae, Brucellaceae, and Micrococcaceae, and decreased Veillonellaceae in schizophrenia patients. Xu et al. (2020) reported increased Sphingomonadaceae and decreased Alcaligenaceae, Enterococcaceae, Leuconostocaceae, and Erythrobacteraceae.

At the genus level, different studies have identified various bacterial taxa. Shen et al. (2018) found significantly higher relative abundance of Succinivibrio, Megasphaera, Collinsella, Clostridium, Klebsiella, and Methanobrevibacter, and lower abundance of Blautia, Coprococcus, and Roseburia in schizophrenia patients compared to healthy controls. Zhao et al. (2019) reported higher Bifidobacterium, Prevotella, and Megamonas, and lower Bacteroides and Faecalibacterium in a small sample study. Nguyen et al. (2019) found increased Anaerococcus and decreased Haemophilus, Sutterella, and Clostridium in schizophrenia patients. Xu et al. (2020) reported increased Actinomycetales, Sphingomonadales, Sphingomonadaceae, Eggerthella, and Megasphaera, and decreased Erythrobacterales and Alcaligenaceae. Li et al. (2020) found decreased Lactococcus and Streptococcus faecalis. A recent study identified the absence of certain gut microbes in schizophrenia patients that are relatively abundant in healthy controls, including Cyanobacteria at the phylum level; Pasteurellaceae, Cytophagaceae, and Morganellaceae at the family level; Acetobacter, Haemophilus, Turicibacter, and Obesumbacterium at the genus level; and Streptococcus equinus, Coprococcus species, and Streptococcus sanguinis at the species level (Manchia et al., 2021).

2.2 Causes and Applications of Gut Microbiota Differences in Schizophrenia

Differences in gut microbiota among schizophrenia patients are influenced by multiple factors. On one hand, gut microbiota in schizophrenia patients originates from early colonization, primarily from birth canal microbiota, delivery environment microbiota, and breast milk microbiota (Ferretti et al., 2018; Singh et al., 2017). These early-colonizing microbes exhibit structural stability in schizophrenia patients' intestines, long-term influencing host central nervous system and immune system function, contributing to individual vulnerability to schizophrenia, and creating significant differences from healthy individuals'

gut microbiota structure. On the other hand, inflammatory responses constitute an important factor causing gut microbiota differences in schizophrenia patients. Clinical studies have found abnormal elevation of immune function in schizophrenia patients, with abnormally increased pro-inflammatory cytokines in blood and brain, indicating a systemic low-grade inflammatory state (Cai et al., 2020; Pedraz-Petrozzi et al., 2020; Upthegrove & Khandaker, 2019). Diffuse low-grade inflammation affects the gut, reducing microbiota ecological diversity. This process is not unidirectional; Clostridium species that produce the anti-inflammatory short-chain fatty acids (SCFAs) are affected by inflammation, leading to reduced SCFA production, which in turn reinforces the inflammatory state (Morgan et al., 2012). Additionally, antipsychotic medications significantly impact gut microbiota in schizophrenia patients. One study found that patients with poor antipsychotic treatment response showed greater differences in gut microbiota, with Lactobacillaceae showing the largest variation across schizophrenia patient subgroups with different treatment responses. The number of intestinal Lactobacillus after treatment was positively correlated with schizophrenia symptom severity (Schwarz et al., 2018). Current research confirms that gut microbiota abnormalities are common in schizophrenia patients, and some studies have identified certain gut microbes as potential biomarkers for distinguishing schizophrenia patients from healthy populations, though the influence of other external factors and treatments (e.g., antipsychotic medications) requires further investigation.

Regarding the application of gut microbiota abnormalities in schizophrenia diagnosis, Shen et al. (2018) identified 12 gut microbial taxa that could serve as biomarkers to differentiate schizophrenia patients from controls, including Gammaproteobacteria at the class level, Enterobacteriales at the order level, and Bacteroides fragilis at the species level. A mouse model study found that gut microbiota including Bifidobacteriaceae, Brucellaceae, Pasteurellaceae, Aerococcaceae, and Rikenellaceae were sufficient to distinguish patient and control groups (Zheng et al., 2019). However, whether these differences can provide new methods and perspectives for auxiliary diagnosis and treatment of schizophrenia requires larger-scale longitudinal studies to infer causal relationships. Additionally, evidence suggests that dysbiosis of gut microbiota composition in schizophrenia patients (including decreased microbial diversity indices) is associated with specific schizophrenia phenotypes, symptom severity, brain structural and functional abnormalities, cognitive deficits, and treatment response (Bioque et al., 2020; Guo et al., 2021; Zeng et al., 2021). Among these, brain structure and cognitive function, as important assessment indicators for schizophrenia, have received increasing attention in relation to gut microbiota.

3.1 The Relationship Between Gut Microbiota and Brain Structure and Function

Gut microbiota may be linked to individual brain structure and function. Beyond the aforementioned evidence regarding early microbiota colonization and

immune-mediated microbiota-gut-brain axis effects on the central nervous system, studies in mouse models and healthy populations support this hypothesis (Tillisch et al., 2017; Ong et al., 2018). In mouse studies, Ong et al. (2018) collected diffusion tensor imaging (DTI) data from four groups of mice fed standard diet (control), high-fat diet, high-fiber diet, and high-protein low-carbohydrate diet, while performing 16S rRNA gene sequencing of the V3-V4 region of fecal samples. Results showed significant changes in potential white matter structural integrity across different dietary groups, with further analysis demonstrating that microbiota composition could potentially predict changes in white matter structural integrity. In a study of healthy humans, Tillisch et al. (2017) performed 16S rRNA analysis of fecal samples from 40 healthy women while obtaining brain magnetic resonance imaging data. Gut microbiota results identified two groups with high relative abundance: high Bacteroides group and high Prevotella group. During emotion induction tasks, negative emotional pictures had significant negative effects on the high Prevotella group, while positive emotional pictures showed no significant difference between groups. In the high Prevotella group, participants with smaller hippocampal volume (a brain region related to emotion regulation) showed greater responses to negative pictures, suggesting that reduced hippocampal volume may be associated with increased emotional arousal. These findings indicate a connection between gut microbiota and brain structure and function, with changes in the relative abundance of dominant Firmicutes and Bacteroides potentially related to brain volume in specific regions.

3.2 The Relationship Between Gut Microbiota and Brain Structure and Function in Schizophrenia Patients

As previously discussed, gut microbiota can influence brain structure and function through the microbiota-gut-brain axis, and this effect also exists in schizophrenia patients. Current research shows that levels of certain gut microbiota-related biomarkers are associated with regional brain volume abnormalities in schizophrenia patients. For example, the kynurenine-to-tryptophan ratio is related to reduced volume of the dorsolateral prefrontal cortex, and serum brain-derived neurotrophic factor (BDNF) levels correlate with bilateral hippocampal volume (Ahmed et al., 2021; Kindler et al., 2020). Currently, research on the relationship between gut microbiota composition and brain structure and function in schizophrenia patients remains limited, but existing studies have found evidence of correlations. We searched Chinese databases (CNKI, Wanfang, VIP) using combinations of keywords including "schizophrenia," "mental illness" with "gut microbiome," "gut microbiota," and "brain structure," "brain function," "brain gray matter," "brain white matter," "MRI," "DTI." We then searched international databases (Web of Science, PubMed, Cochrane Library, Science Direct) using combinations of "schizophrenia," "psychiatry" with "gut microbiome," "gut microbiota," "gastrointestinal microbiome," "gastrointestinal microbiota" and "brain structure," "brain function," "brain imaging," "grey matter," "white matter," "MRI," "DTI." We

searched titles, keywords, and abstracts with a cutoff date of December 2021, identifying three empirical studies meeting inclusion criteria.

Table 2. Summary of Studies on Gut Microbiota-Brain Imaging Correlations in Schizophrenia

Study	Participants	Intervention	Measurement	Key Findings
Wu (2019)	21 SCZ inpatients, 30 HCs	None (hospitalized)	16S rRNA, SIEMENS 3.0T Prisma MRI	SCZ showed decreased ALFF in bilateral occipital and posterior parietal lobes, increased ALFF in bilateral medial frontal, lateral prefrontal, and medial temporal lobes; decreased ReHo in superior temporal gyrus and bilateral occipital lobe. Actinobacteria and Coriobacteriia abundance positively correlated with lateral prefrontal and right middle frontal gyrus ALFF.

Study	Participants	Intervention	Measurement	Key Findings
Ma et al. (2020)	40 first-episode SCZ (FSCZ), 45 chronic medicated SCZ (TSCZ), 69 HCs	None (first-episode vs chronic)	16S rRNA, structural MRI	No total gray matter volume difference between SCZ and HCs, but right middle frontal gyrus gray matter volume increased in SCZ. Actinobacteria and Veillonellaceae abundance positively correlated with right middle frontal gyrus volume in FSCZ but not TSCZ.

Li et al. (2021)	38 SCZ, 38 HCs	None	16S rRNA, resting-state fMRI	No α diversity difference between groups. SCZ showed altered α diversity evenness and Shannon index correlated with gray matter volume in insula, inferior frontal operculum, and right postcentral gyrus. Lactococcus and Roseburia decreased, Veillonella increased.

Note: GM, gut microbiota; ALFF, amplitude of low-frequency fluctuation; ReHo, regional homogeneity.

These studies consistently found significantly increased relative abundance of Actinobacteria and some of its subordinate taxa in schizophrenia patients, along with some Proteobacteria subgroups, consistent with previous findings (Li et al., 2020; Shen et al., 2018; Xu et al., 2020; Zhao et al., 2019). Neuroimaging results demonstrate that the relationship between gut microbiota and brain in schizophrenia patients primarily manifests in two aspects: brain structure and brain function.

3.2.1 The Relationship Between Gut Microbiota and Brain Structure

Regarding the relationship between gut microbiota and brain structure, current research has primarily identified associations between microbiota composition and regional gray matter volume. In terms of relative abundance, Ma et al. (2020) conducted an exploratory study finding that first-episode schizophrenia patients showed significantly reduced relative abundance of Escherichia coli, Actinobacteria, and Clostridium compared to healthy controls. Additionally, chronic medicated schizophrenia patients showed significantly increased relative abundance of Peptostreptococcaceae and Veillonella, suggesting that antipsychotic medications influence gut microbiota. Further analysis revealed that Actinobacteria and Veillonella abundance positively correlated with abnormal

right middle frontal gyrus gray matter volume in first-episode patients, but this correlation was not observed in chronic medicated patients. This implies a connection between gut microbiota and brain structure in schizophrenia patients that is influenced by antipsychotic medication. Regarding microbiota diversity, a recent study on the relationship between gut microbiota and brain structure in schizophrenia found that α diversity was significantly positively correlated with gray matter volume in the insula, pars opercularis of the inferior frontal gyrus, and right postcentral gyrus (Li et al., 2021).

3.2.2 The Relationship Between Gut Microbiota and Brain Function

Regarding the relationship between gut microbiota and brain function, Wu (2019) used resting-state functional magnetic resonance imaging to examine the amplitude of low-frequency fluctuation (ALFF) and regional homogeneity (ReHo) in schizophrenia patients, exploring relationships between brain function and significantly increased gut microbes. Results showed that Actinobacteria and Veillonella abundance was significantly positively correlated with ALFF values in the lateral prefrontal cortex and right middle frontal gyrus. The relative abundance of Acidaminococcus (order Clostridiales) was positively correlated with ALFF values in the occipital lobe but significantly negatively correlated with the temporal lobe. ReHo value correlation analysis with gut microbiota revealed that Actinobacteria and Coriobacteriia abundance in schizophrenia patients was significantly positively correlated with ReHo values in the dorsolateral prefrontal cortex but negatively correlated with the inferior and middle temporal gyri. These findings suggest that the relationship between gut microbiota and brain function in schizophrenia patients is primarily reflected in the frontal and temporal lobes, which are responsible for motor function, language, memory, and other activities. Additionally, significantly increased Coriobacteriia in schizophrenia patients was positively correlated with dorsal prefrontal cortex and sensorimotor cortex, and negatively correlated with medial superior frontal gyrus and temporal lobe. Dorsal prefrontal cortex dysfunction is associated with negative symptoms and cognitive impairment in schizophrenia. Most Coriobacteriia are pathogenic, and Collinsella within Coriobacteriia is associated with colorectal cancer, suggesting that increased Coriobacteriia abundance may be a risk factor for schizophrenia. Li et al. (2021) examined the relationship between gut microbiota diversity and brain function in schizophrenia patients, finding that the Shannon index of α diversity was positively correlated with ReHo values in bilateral cortices, bilateral lingual gyri, left superior occipital cortex, and right superior parietal cortex. The evenness of α diversity was positively correlated with ReHo values in the right cuneus, bilateral fusiform gyri, left postcentral gyrus, and left parietal cortex, suggesting that brain function abnormalities in schizophrenia may be related to altered gut microbiota α diversity.

3.3 Mechanistic Hypothesis of Gut Microbiota Effects on Brain Structure in Schizophrenia

The above evidence suggests that the potential role of gut microbiota in schizophrenia is related to alterations in brain structure. Although the specific mechanisms remain unclear, existing evidence reveals possible pathways. Schizophrenia patients exhibit severe neurotransmitter dysregulation, and central nervous system development is associated with neurotransmitter levels. Gut microbiota can identify and produce chemical substances that affect the nervous system through multiple pathways (Jameson & Hsiao, 2018). Gut microbiota metabolites include many important neurotransmitters and neurotransmitter precursors (Strandwitz, 2018; Williams et al., 2014). Although most neurotransmitters produced by gut microbiota cannot cross the blood-brain barrier, their precursors such as tryptophan and tyrosine can cross the gut-brain barrier, influencing brain serotonin and dopamine levels (Jameson & Hsiao, 2018). Serotonin and dopamine dysregulation is common in schizophrenia and other mental disorders (Stępnicki et al., 2018). This dysregulation may represent a potential mechanistic pathway through which gut microbiota contributes to schizophrenia pathology (Zhang et al., 2015). Based on clinical evidence regarding gut microbiota effects on neurodevelopment, we propose the following mechanistic hypothesis regarding how gut microbiota influences brain structure in schizophrenia patients (Figure 1).

Figure 1. Mechanistic Hypothesis of Gut Microbiota Effects on Brain Structure in Schizophrenia

Note: MGBA, microbiota-gut-brain axis; Gut Microbiota; Dopamine; 5-HT, serotonin; Neuron; Synapse; Microglia; Tryptophan; Kynurenine Pathway; Dorsal Lateral Prefrontal Cortex; Hippocampus; Brain Structure; SCFA, short-chain fatty acids; BDNF, brain-derived neurotrophic factor.

First, the immune-mediated pathway may be an important route through which gut microbiota influences brain structure in schizophrenia patients. Gut microbiota dysbiosis may lead to increased inflammatory mediators and decreased protective mediators, resulting in neuronal and synaptic damage as a potential factor contributing to brain structural abnormalities in schizophrenia. Inflammatory factors produced by gut microbiota can directly affect the brain or activate the hypothalamic-pituitary-adrenal (HPA) axis (Rodrigues-Amorim et al., 2018). Evidence indicates that Bacteroides intervention can reduce HPA axis response to restraint stress in rats by decreasing intestinal permeability (Ait-Belgnaoui et al., 2012). Both prokaryotic and eukaryotic microbes produce receptors for various neurohormones, and gut microbiota can produce bioactive endocrine hormones dopamine and norepinephrine in quantities sufficient to affect host neurophysiological activity (Jadhav et al., 2018; El Aidy et al., 2017). Additionally, germ-free mice transplanted with fecal microbiota from schizophrenia patients showed increased basal extracellular dopamine in the prefrontal cortex and increased serotonin in the hippocampus, along with hyperactivity

symptoms (Zhu, Guo, et al., 2020).

Second, the SCFA pathway may also play an important role in gut microbiota effects on brain structure in schizophrenia patients. SCFAs, including acetate, propionate, and butyrate, are primarily synthesized by gut microbiota metabolism and are considered important in neuroimmunoendocrine regulation. Increased α diversity of gut microbiota in schizophrenia patients is positively correlated with serum SCFA concentrations and shows elevated immune activation levels (Zhu, Ju, et al., 2020). Additionally, abnormal levels of SCFAs such as acetate and propionate can cause widespread metabolic and neurological dysfunction, particularly affecting microglial maturation (Bauer et al., 2019).

Third, the kynurenine pathway represents another important mechanism. Gut microbiota can participate in tryptophan metabolism, affecting central nervous system function in schizophrenia patients. Through the kynurenine pathway, gut microbiota can influence brain 5-hydroxytryptamine levels, further affecting emotion and cognitive function regulation (Jenkins et al., 2016). After transplanting schizophrenia patient fecal microbiota into germ-free mice, increased extracellular dopamine concentrations and elevated serotonin levels were observed in prefrontal cortex samples. This dysregulation of tryptophan metabolism through activation of the kynurenine pathway caused schizophrenia-like behaviors in mice (Chiappelli et al., 2014). Kindler et al. (2020) found that the kynurenine-to-tryptophan ratio was significantly higher in schizophrenia patients' prefrontal cortex compared to normal controls and negatively correlated with dorsolateral prefrontal cortex volume. This may result from pro-inflammatory factors causing peripheral tryptophan conversion to kynurenine, affecting astrocytic enzyme synthesis activity, leading to dorsolateral prefrontal cortex volume loss and attention impairment. Gut microbiota can regulate 95% of intestinal tryptophan metabolism through the kynurenine pathway, which plays an important role in brain kynurenine synthesis, thereby affecting brain structure and cognitive function in schizophrenia patients (Schwarcz et al., 2012; Wang et al., 2019; Zhu, Guo, et al., 2020).

Finally, the BDNF pathway is also important. Gut microbiota-derived metabolites may affect BDNF and other proteins important for cognition in the central nervous system, thereby influencing host behavior (Munawar et al., 2021; Rogers et al., 2016). BDNF is a crucial neurotrophic factor in brain development, involved in myelination and synaptic pruning (Lv et al., 2017). Schizophrenia is typically accompanied by BDNF alterations, with decreased BDNF levels observed in the hippocampus and plasma, which is associated with cognitive dysfunction such as learning and memory impairments (Man et al., 2018). Ahmed et al. (2021) found that serum BDNF levels in schizophrenia patients were significantly correlated with left and right hippocampi, providing evidence for an association between brain volume and BDNF levels. Although current results have not directly confirmed the role of the BDNF pathway between gut microbiota and brain structure in schizophrenia patients, studies have found that gut microbiota can affect schizophrenia risk by influencing tyrosine kinase recep-

tor B (TrkB) and BDNF levels in the hippocampus (Gupta & Hoffman, 2021). Future research should examine correlations between gut microbiota structure (or individual microbial species such as Lactobacillus) and BDNF levels while also assessing brain structure to explore how the BDNF pathway influences the relationship between gut microbiota composition and brain structure in schizophrenia patients.

4. The Relationship Between Gut Microbiota and Clinical Manifestations in Schizophrenia

Cognitive impairment represents the third major symptom cluster in schizophrenia patients, beyond positive and negative symptoms (Meltzer & McGurk, 1999). Cognitive impairment in schizophrenia includes poor social and personal cognitive function, primarily manifested as deficits in attention, memory, language, executive function, and thinking (Fett et al., 2011; Green et al., 2019). Although current antipsychotic medications effectively treat positive and negative symptoms, they show limited efficacy for cognitive impairment, necessitating further investigation into its causes (Hori et al., 2006). Current research suggests that cognitive impairment in early-stage schizophrenia is related to inflammatory processes, with gut microbiota participating through effects on glucocorticoids and immune mediators (Cabrera et al., 2016; Cussotto et al., 2018). Abnormal activation in multiple brain regions and structural brain abnormalities are considered related to cognitive impairment and clinical symptoms. Previous studies have reported that gut microbiota may participate in several neurodevelopmental pathways in schizophrenia pathogenesis, suggesting that the relationship between gut microbiota composition and cognitive impairment as well as clinical symptoms can be explained by the microbiota-gut-brain axis theory (Sharon et al., 2016). Additionally, genetic background, brain-derived neurotrophic factor, and abnormal immune function are considered related to cognitive impairment in schizophrenia, with gut microbiota effects on BDNF and immune function suggesting possible connections with cognitive impairment (Rogers et al., 2016; Zheng et al., 2019).

Existing research shows associations between gut microbiota and cognitive function in schizophrenia patients (Schwarz et al., 2018; He et al., 2018; Li et al., 2021). In a clinical study, Schwarz et al. (2018) found that first-episode schizophrenia patients had significantly increased Lactobacillus compared to healthy controls, which negatively correlated with psychosocial functioning scores. He et al. (2018) studied high-risk and ultra-high-risk schizophrenia groups, finding that participants with heterogeneous gut microbiota cluster analysis showed lower Global Assessment of Functioning (GAF-M) scores. Li et al. (2021) found that perceptual disturbances in schizophrenia patients were associated with altered gut microbiota α diversity; for example, α diversity may be related to visual hallucinations, potentially mediated by functional brain activity in the calcarine fissure.

Furthermore, research has identified associations between gut microbiota com-

position and clinical symptoms in schizophrenia patients. He et al. (2018) found that when high-risk and ultra-high-risk schizophrenia participants were divided into cluster-outside and cluster-inside groups based on gut microbiota cluster analysis, the cluster-outside group showed higher scores for positive symptoms, negative symptoms, and dissociative symptoms. Schwarz et al. (2018) also found that the abundance of certain gut microbiota, including Lactobacillus, Lactobacillaceae, Lactococcaceae, and Bacteroides, was significantly positively correlated with schizophrenia symptom severity. Yuan et al. (2021) found that the relative abundance of Lachnospiraceae and Firmicutes was significantly positively correlated with negative symptom (PANSS-FSNS) scores. These findings indicate that increased relative abundance of certain bacterial genera in schizophrenia patients is associated with clinical symptoms.

5. Future Research Directions

Based on microbiota-gut-brain axis theory and related research evidence, we know that the relationship between abnormal gut microbiota and brain structure and function in schizophrenia patients can be traced to early life, with continuous influence throughout later periods. Previous research has focused on cross-sectional correlational studies, which can only explore associations between the two factors. Therefore, longitudinal studies are needed to better reveal causal relationships. Regarding study populations, given the importance of high-risk groups for schizophrenia prevention and early treatment, further research should target these high-risk populations. Although preliminary studies have identified associations between specific gut microbiota and particular brain regions, small sample sizes and regional factors limit result generalizability, necessitating large-sample studies for validation, identification of appropriate measurement indicators, and statistical standardization to provide auxiliary means for comprehensive schizophrenia diagnosis. Additionally, examining brain structure in schizophrenia patients must be linked to cognitive function. Since cognitive impairments such as memory deficits do not recover with symptom improvement, whether this irreversible damage is related to gut microbiota requires further investigation (Guo et al., 2019).

Furthermore, previous schizophrenia prevention and treatment strategies have primarily been based on dopamine and serotonin hypotheses, with limited efficacy (e.g., no significant effect on cognitive impairment) and problems including disease recurrence and severe side effects (Seeman, 2021; Stahl, 2018; Cadinu et al., 2018; MacKenzie et al., 2018; Gillespie et al., 2017). Microbiota-based treatments for schizophrenia grounded in the microbiota-gut-brain axis hypothesis have shown preliminary application, with some effectiveness in alleviating side effects of traditional antipsychotics, such as treating gastrointestinal diseases commonly comorbid with schizophrenia (Dickerson et al., 2014). Additionally, although probiotic and prebiotic treatments have not significantly improved positive and negative symptoms, they may serve as adjunctive therapy for cognitive impairment (Mörkl et al., 2020; Ng et al., 2019; Szeligowski et al., 2020).

Currently, gut microbiota intervention for schizophrenia treatment remains in preliminary stages, requiring exploration of more specific treatment protocols and clinical intervention studies to further investigate how gut microbiota influences brain structure, function, and clinical manifestations, and to provide more comprehensive approaches for schizophrenia prevention and treatment.

6. Conclusion

This review examined recent research on abnormal gut microbiota in schizophrenia patients and its relationship with brain structure, function, and clinical manifestations. The main findings are: (1) Regarding gut microbiota composition differences, schizophrenia patients show reduced microbial diversity and altered relative abundance of key taxa compared to healthy individuals, primarily caused by low-grade inflammatory responses induced by schizophrenia. Studies in first-episode schizophrenia patients support this view. Additionally, antipsychotic medications have some impact on gut microbiota but may not cause major compositional changes. (2) Regarding the relationship between gut microbiota and brain structure and function, both the relative abundance and diversity of gut microbiota in schizophrenia patients correlate with gray matter volume in abnormal brain regions. For example, Actinobacteria and Veillonellaceae abundance positively correlate with gray matter volume in the right middle frontal gyrus in first-episode schizophrenia patients. Brain imaging results suggest that functional abnormalities may be related to altered gut microbiota α diversity. (3) Regarding mechanistic hypotheses, we propose that gut microbiota may influence brain structure in schizophrenia patients through immune-mediated, SCFA, kynurenine, and BDNF pathways. (4) Regarding relationships with cognitive function and clinical symptoms, Lactobacillus abundance in schizophrenia patients shows significant positive correlations with cognitive impairment and clinical symptoms, and changes in gut microbiota α diversity may be associated with visual hallucinations.

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