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The Role of Physical Activity in Gut–Brain Axis Regulation and Cognitive Enhancement in Schizophrenia

Patrycja Niczyporuk[2] [PN], ORCID https://orcid.org/0009-0001-5834-5277

E-mail: 39916@student.umb.edu.pl

Izabela Zajkowska[1] [IZ], ORCID https://orcid.org/0009-0002-8526-7339

E-mail: zajkowska.izabela@wp.pl

Wiktor Warych[1] [WW], ORCID https://orcid.org/0009-0003-2569-6833

w.warych26@gmail.com

Julia Baran[2] [JB], ORICID https://orcid.org/0009-0005-9569-3149

barjul99@gmail.com

Karolina Wojciechowska[1] [KW], ORCID https://orcid.org/0009-0001-7048-1335

E-mail: karolina8wojciechowska@gmail.com

Julia Martowska[1] [JM], ORCID https://orcid.org/0009-0006-2804-5368

E-mail: julia.wiaterek@gmail.com

[1] Śniadeckiego Voivodeship Hospital in Bialystok, ul. M. C. Skłodowskiej 26, 15-278 Białystok, Poland

[2] University Clinical Hospital in Białystok, ul. M. C. Skłodowskiej 24a, 15-276 Białystok, Poland

Corresponding Author: Izabela Zajkowska, zajkowska.izabela@wp.pl

Background: Recent research highlights the growing importance of the gut–brain axis in neuropsychiatric disorders, including schizophrenia. Particular attention is given to microbial dysbiosis and its influence on neurotransmitter dynamics, systemic inflammation, and cognitive function. Schizophrenia is marked by progressive impairments in attention, working memory, and executive function, often accompanied by hippocampal atrophy—deficits not fully addressed by standard pharmacotherapy.

Aim: This review aims to elucidate the mechanisms through which gut microbiota influence neurotransmitter synthesis and cognitive regulation in schizophrenia, and to evaluate the role of exercise as a potential modulator of both microbiota composition and neuroplasticity.

Material and Methods: A systematic literature review was conducted on March 18, 2025, using a Python-based script to extract relevant studies from PubMed. The search focused on the interactions between schizophrenia, gut microbiota, neurotransmitter systems, and the effects of exercise-based interventions.

Results: Evidence from clinical and preclinical studies indicates that alterations in gut microbiota significantly affect the synthesis of neuroactive compounds such as serotonin, GABA, and dopamine. Moreover, structured exercise programs have been shown to improve cognitive function, increase hippocampal volume, and positively modulate gut microbial composition, suggesting synergistic benefits when combined with conventional treatment.

Conclusions: Targeted interventions addressing the gut–brain axis—through microbiota modulation and exercise therapy—represent promising adjunctive strategies in the treatment of schizophrenia. These approaches may enhance neurocognitive outcomes and support more personalized, holistic models of care.
Keywords: schizophrenia, brain-gut axis, ; Microbiota, neurotransmitters, activity

1. Introduction

Schizophrenia affects about 1% of people worldwide and presents a complex mix of positive, negative, and cognitive symptoms (Schizophrenia 2025). Traditional antipsychotics mainly focus on correcting dopamine imbalances, yet many patients don’t achieve optimal results (Amato et al. 2019). This shortfall has sparked interest in exploring other pathways, especially those linked to the gut–brain axis.

The gut–brain axis is a two-way communication network connecting the gut microbiota to the central nervous system, playing a crucial role in regulating neurotransmitter systems. Recent evidence suggests that dysbiosis—characterized by a reduction in beneficial bacteria like Lactobacillus and Bifidobacterium—can disrupt the production and regulation of key

neurotransmitters (such as dopamine, serotonin, glutamate, and GABA), which are vital in the development of schizophrenia (Carabotti et al. 2015). Moreover, microbial metabolites like short-chain fatty acids and alterations in tryptophan metabolism have been found to affect neuronal excitability and receptor expression, potentially altering central neurotransmission (Xu et al. 2025).

Based on these findings, new therapeutic strategies aimed at restoring a balanced gut microbiome—using probiotics, prebiotics, or fecal microbiota transplantation—are emerging as promising additions to conventional antipsychotic treatments (Sahle et al. 2024). This review brings together current insights into how the gut influences neurotransmitter regulation in schizophrenia and explores the potential benefits of targeting the gut–brain axis. By combining discoveries from microbiology, neurochemistry, and clinical psychiatry, we hope to develop a more comprehensive model of schizophrenia that could lead to better, personalized treatment strategies.

The purpose of research

The primary objective of this review is to elucidate the pathways through which gut microbiota influence neurotransmitter synthesis and regulation in schizophrenia, with a focus on the relationship between microbial dysbiosis and alterations in key neurotransmitters such as serotonin, GABA, and dopamine, as well as the potential integration of microbiota-targeted approaches with traditional pharmacological treatments to enhance clinical outcomes in schizophrenia.

2. Research materials and methods

On March 18, 2025, we conducted a systematic literature search using a PubMed scraping script in a Python environment. The search incorporated keywords such as “schizophrenia,” “gut–brain axis,” “microbiota,” and “neurotransmitters.” The selection criteria were restricted to publications in English, with no limitations on publication dates to ensure comprehensive coverage. The resulting database was screened to include studies addressing the role of gut microbiota in the synthesis and regulation of neurotransmitters and the impact of microbial dysbiosis on inflammatory markers relevant to schizophrenia. Data were extracted and synthesized to provide an integrative overview of current insights and potential therapeutic implications.

Keywords: Schizophrenia; Gut–Brain Axis; Microbiota; Neurotransmitters; Physical Activity;

Shortcuts: IDO - Indoleamine 2,3-dioxygenase, TDO - Tryptophan 2,3-dioxygenase, IFN-γ - Interferon gamma, TNF-α - Tumor necrosis factor alpha, KAT - Kynurenine aminotransferase, KYNA - Kynurenic acid, NMDA - N-Methyl-D-Aspartate, GABA - Gamma-Aminobutyric acid, D2R - Dopamine receptor 2.

3. Research results

3.1. Gut microbiota involved in developing schizophrenia

The microbiota is a group of microorganisms that colonize the human body, and a significant portion of it, as much as 90%, colonizes the small and large intestine. It is estimated that the microorganisms inhabiting the macroorganisms outnumber their cells tenfold. The composition of the microbiota depends both on internal interactions and on the conditions of the organism they colonize (Góralczyk-Bińkowska et al. 2022).

The interaction between the gut microbiota and the CNS has been termed the "microbiota-gut-brain axis." The symbiosis that occurs between the gut microbiota and the host is regulated by a complex network of interactions mediated by metabolites produced by the microorganisms. This is made possible by the peripheral nervous system, which includes a highly innervated neural network. This is called the enteric nervous system (ENS) and facilitates communication between the CNS and the gut (McGuinness et al. 2022).

The relationship that exists between the composition of the gut microbiota and psychiatric disorders is increasingly being considered as one of the predisposing factors for disease. Current projections indicate that the global problem of mental illness is significant and will continue to grow (Moitra et al. 2022). Data illustrating this is the WHO's prediction that depression will become the most common chronic disease in the world by 2030 (Malhi and Mann 2018). Critical to the development of treatment for people with schizophrenia is the understanding of patients' personal, social, and occupational functioning and the use of appropriate psychiatric rehabilitation practices. It is also important to study the etiopathogenesis of these disorders, which can help improve prevention and mental health promotion. The development of new, more effective pharmacological agents to improve the functioning of people with mental disorders is essential.

3.2. Microbiota-Gut-Brain Axis

Through the "microbiota-gut-brain" axis, the gut microbiota may play an important role in the pathogenesis of schizophrenia. This axis may link the microbiome to the CNS through the nervous, endocrine, and immune systems (Pan et al. 2020). Studies of patients with psychiatric disorders have shown dysregulation of inflammation and oxidative stress pathways, tryptophan and kynurenine metabolism, neurotransmitters, and brain plasticity. These disturbances are reflected in changes in the composition and function of the gut microbiota (McGuinness et al. 2022).

In disorders of the gut microbiota, inflammation is observed throughout the body. This can be seen, for example, in the presence of inflammatory markers such as pro-inflammatory cytokines in patients with schizophrenia. In addition to pro-inflammatory cytokines, microglia play an important role in inflammation in the CNS. The picture of patients with schizophrenia may suggest that the disease has features of neurodegeneration, which is closely related to CNS inflammation (Na et al. 2014). Magnetic resonance imaging studies of schizophrenic patients have shown progressive changes in some, in the form of reduced gray matter volume in the frontal and temporal lobes of the brain. There are theories that point to abnormally activated apoptosis as the cause of this phenomenon (Csernansky 2007). Apoptotic changes in the brain and the presence of apoptotic proteins have been implicated in the pathophysiology of diseases such as Parkinson's and Alzheimer's, among others. However, genetic studies report that people with schizophrenia also have active risk alleles associated with apoptosis (Morén et al. 2022).

Essential for proper regulation of gastrointestinal function and communication with the CNS is the ENS, which forms the "gut-brain axis." The gut microbiota plays a key role in modulating the ENS. This axis consists of intestinal glial cells, which are located throughout the gastrointestinal tract and are constantly modulated by the gut microbiota (Collins et al. 2013).

Studies by Collins et al. (2013) and Kabouridis et al. (2015) showed that the absence of gut microbiota in pathogen-free mice leads to a significant reduction in nerve fiber density in the jejunum and ileum. There is also a reduction in the number and density of glial cells compared to conventional mice. The results suggest that the microbiota is critical for the normal development of the intestinal glial network and that its influence is not limited to the early postnatal period, as conventionalization of 4-week-old pathogen-free mice showed restoration of the intestinal glial network (Kabouridis et al. 2015).

Information from the gastrointestinal tract reaches the CNS via sensory fibers of the vagus nerve. This pathway was tested in mice treated orally with saline or live Campylobacter jejuni. It was

shown that mice treated with the pathogen experienced strong neuronal activation in the primary sensory relay nucleus of the vagus nerve, the solitary band nucleus. The choice of Campylobacter jejuni was based on the fact that this infection does not induce circulating inflammatory mediators, confirming that the vagus nerve contributes to CNS activation (Goehler et al. 2005).

3.3. Microbiota in people with schizophrenia

Patients with schizophrenia are significantly more likely to have compositional changes in their microbiota (Pan et al. 2020).

A study by Girdler et al (2019) found that regular physical activity can induce beneficial neuroanatomical changes in people with schizophrenia. Participants in an aerobic exercise program, carried out three times a week for three months, reported significant increases in hippocampal volume and improvements in short-term memory, compared to a control group receiving only occupational therapy. These results confirm that physical training can promote neuroplasticity and be an effective adjunct to the treatment of cognitive symptoms of schizophrenia.

Xiaoqian Ma et al. conducted a study to show the relationship between the gut microbiome and the pathogenesis of schizophrenia and treatment with antipsychotic drugs. They used 16S rRNA gene sequencing to analyze stool samples from 40 patients with a first episode of schizophrenia who were off medication, 85 patients with schizophrenia who were chronically treated with antipsychotics, and 69 healthy controls. The results showed that both patients with a first episode of schizophrenia and patients chronically treated with antipsychotic drugs had distinct changes in the microbial composition of the gut. Differences occurred in the composition of taxa such as Christensenellaceae, Enterobacteriaceae, Pasteurellaceae, Turicibacteraceae at the family level and Escherichia at the genus level compared to the control group. In addition, patients underwent brain magnetic resonance imaging (MRI) to assess brain structure, and it was found that the characteristic microbiota of patients with schizophrenia correlated with the volume of the right middle frontal cortex (Ma et al. 2020).

A study by Yang Shen et al. looked for differences in the gut microbiota of 64 patients with schizophrenia and 53 healthy controls. 16S rRNA sequencing showed that at the species level, there was an increased amount of Proteobacteria in the patients. In addition, at the genus level, a higher abundance of Succinivibrio, Megasphaera, Collinsella, Clostridium, Klebsiella, and

Methanobrevibacter and a significantly reduced abundance of Blautia, Coprococcus, Roseburia were found compared to the control group. However, the main goal of this study was to identify specific biomarkers of schizophrenia that could be used to develop a non-invasive microbiota-based diagnostic marker. The Borut feature selection algorithm was used for this purpose. The results showed that Gammaproteobacteria is an important biomarker at the class level, Enterobacteriales at the order level, Alcaligenaceae, Enterobacteriaceae and Lachnospiraceae at the family level, Acidaminococcus, Phascolarctobacterium, Blautia, Desulfovibrio and Megasphaera at the genus level, and Plebeius fragilis at the species level (Shen et al. 2018).
In addition, studies suggest that changes in the microbiota may become not only a diagnostic indicator, but also an indicator of disease progression in people with schizophrenia. Rubing Pan et al. analyzed 87 stool samples from patients with acute and remission schizophrenia in their cohort study. They looked for changes in the microbiome between remission and onset of illness that could become biomarkers of disease progression. Analysis of stool samples showed that Clostridium, genus Peptostreptococcaceae and family Clostridiaceae were increased in patients in remission compared to patients in the acute phase of schizophrenia. In addition, the genus Clostridium was found to be negatively correlated with Positive and Negative Syndrome Scale (PANSS) scores in patients in remission, suggesting that a change in the microbiota is associated with patient improvement (Pan et al. 2020).

3.4. Microbiota-Related Neurotransmitters

Communication between the human gastrointestinal tract and the CNS relies on information transmitted by the immune system, the vagus nerve, and neurotransmitters produced by the microbiota. Microbes residing in the gastrointestinal tract can produce a variety of neurotransmitters, including dopamine, norepinephrine, serotonin, and GABA. Changes in the composition of the microbiota affect the levels of neurotransmitters in the body (Strandwitz 2018). Different strains of bacteria have been shown to produce different neurotransmitters: dopamine production is responsible for Escherichia spp. (Strandwitz 2018), Bacillus spp. (Detection of neurotransmitter amines in microorganisms 2000), serotonin Escherichia spp. (Shishov et al. 2009), Candida spp. and Klebsiella spp. (Kuley et al. 2024), among others. Other strains involved in neurotransmitter production include Lactobacillus (Siragusa et al. 2007) and Bifidobacterium (Barrett et al. 2012), which can produce GABA and acetylcholine (Stanaszek et al. 1977).

Table 1. Neurotransmitters and the bacteria that produce them

Neurotransmitter	**BacteriaProducingNeurotransmitter**	**Function in the Body**	**Additional Notes**
Dopamine	*Escherichia spp.*, *Bacillusspp.*	Motivation, reward, moodregulation	Also involved in controlling movement. Dopamine deficiency is associated with disorders like Parkinson's disease. Microbiotamay influence itsavailabilitythroughgut-braincommunication.
Serotonin	*Escherichia spp.*, *Candida spp.*, *Klebsiella spp.*	Regulation of mood, sleep, and appetite	About 90% of serotonin is produced in the gut. Its synthesis is influenced by gut bacteria, and imbalances are associated with depression and anxiety.
GABA	*Lactobacillusspp.*, *Bifidobacteriumspp.*	Inhibitory neurotransmitter that calms neural activity	It plays a crucial role in reducing anxiety and promoting relaxation. Gut bacteria involved in GABA production may have therapeutic potential for anxiety and stress-related disorders.

Acetylcholine	*Lactobacillusspp.*, *Bifidobacteriumspp.*	Learning, memory, and muscle activation	A key neurotransmitter for neuromuscular communication. Gut microbiota may indirectly support its synthesis, influencing cognition and muscle function.

3.4.1. Serotonin

Mood, cognitive processes, anxiety, learning, memory, and sleep are all modulated in the CNS by the binding of serotonin to 5-HT receptors. Serotonin deficiency in the CNS can result in disorders such as depression, schizophrenia, mood disorders and autism (Pourhamzeh et al. 2021).

While serotonin exerts its widespread effects on physiological processes throughout the body, 90–95% of serotonin is found in the gastrointestinal tract, specifically in enterochromaffin cells (Gershon and Tack 2007). Serotonin levels are dependent on the composition of the gut microbiota, as shown by a growing body of research, such as in germ-free (GF) mice, which showed a significant decrease in blood and colon serotonin levels compared to a control group (Wikoff et al. 2009).

Interestingly, no serotonin-producing bacterial strains have been identified in the gut. Serotonin levels appear to be dependent on microbiome-produced short-chain fatty acids (SCFAs) and secondary bile acids, which increase serotonin production through increased expression of tryptophan hydroxylase in enterochromaffin cells (Yano et al. 2015).

They also showed that serotonin release from enterochromaffin neurons is important for the development and survival of dopaminergic neurons. This highlights the role of serotonergic neurons in the formation of mature networks in the enteric nervous system. Immunohistochemical studies in mouse models without microbiota revealed that serotonergic networks were almost absent. A gradual restoration of this network occurred after secondary colonization with the gut microbiota. The presence of microbiota proved crucial for the maintenance of these networks, as antibiotic use led to the disappearance of serotonin immunoreactivity in the intestines of the mice studied (De Vadder et al. 2018).

3.4.2. Gamma-Aminobutyric acid (GABA)

GABA functions as an inhibitory neurotransmitter in the CNS, reducing excessive neuronal activity, and its disrupted neurotransmission has been linked to behavioral, pain, and sleep disorders, as well as increased anxiety and psychotic symptoms in people with schizophrenia (Wikoff et al. 2009).

Supporting this, a study in which GF mice were transplanted with the gut microbiota of patients with schizophrenia showed that such mice exhibited increased glutamine and GABA, along with decreased glutamate, in the hippocampus (Ma et al. 2020).

To highlight the influence of the microbiota on GABA neurotransmitter metabolism, we would like to make a connection. Schizophrenic patients have been shown to have lower levels of Bacteroides and Streptococcus in their gut microbiota composition. At the same time, these bacteria are associated with glutamate and GABA metabolism. A study by Strandwitz et al. (2018) found that Bacteroides is responsible for producing large amounts of GABA (Strandwitz et al. 2018).

Changing dietary habits that also affect gut microflora has also been shown to affect GABA production levels. In children with drug-resistant epilepsy, a ketogenic diet has been shown to increase cerebrospinal fluid GABA levels and is associated with a more than 90% reduction in hyperpnea (Dahlin et al. 2005).

It is also worth noting that obesity affects 40–60% of patients with severe psychiatric disorders. Obesity in patients with schizophrenia is associated with neurostructural changes and affects psychiatric outcomes as well as physical health and mortality, regardless of etiology (Perry et al. 2021).

In a study by Kootte et al. (2017), GABA was found to be the most altered neurotransmitter in obese patients receiving allosteric fecal transplantation from lean donors. Changes in the amount of Lactobacillus brevis were also found in obese individuals, which is particularly noteworthy because this species is responsible for GABA production (Kootte et al. 2017).

3.4.3. Dopamine

One of the most established theories in psychiatry is that disorders in the dopaminergic system are the cause of schizophrenia. Particular attention is paid to the mesolimbic pathway, where dopamine activity is increased, leading to psychosis. Dopamine itself is associated in the nervous system with motivation and the reward center (Stahl 2018).

Dopamine synthesis occurs by several pathways. It can occur by hydroxylation of tyrosine to L-dihydroxyphenylalanine (L-DOPA), which is then decarboxylated to dopamine. In the presence of dopamine, dopamine β-hydroxylase is converted to norepinephrine and epinephrine. Another route of dopamine production is synthesis by certain Bacillus and Serratia species in the gastrointestinal tract, making dopamine availability dependent on the gut microflora (Dicks 2022). This suggests a strong relationship between the gut microbiome and dopamine.

Provatella and Bacteroides, which belong to the Bacteroidetes genus, produce metabolites that have been linked to the effect of dopamine on synaptic gap activity. A study by Hartstra et al. (2020) found that administration of Bacteroides uniformis in a fecal microbiota transplant increased dopamine binding by dopamine transporter presynaptic membrane proteins in the striatum. Prevotellacopri had the opposite effect. The dopamine transporter regulates the amount of dopamine in the CNS by recycling and storing dopamine in vesicles at presynaptic terminals. This allows for its subsequent release and modulation. The mechanism by which the metabolites of these types of bacteria affect the dopamine transporter is not known; nevertheless, they may become candidates for regulating this protein through the afferent fibers of the vagus nerve (Hamamah et al. 2022).

On the other hand, administration of Lactobacillus and Bifidobacterium, which are commonly used as probiotics, reduced anxiety, depressive behavior and stress responses in GF mice. In the same mice, adrenocorticotropic hormone (ACTH) and corticosterone levels were measured in response to stress prior to probiotic administration. ACTH and corticosterone levels were significantly elevated compared to the control group (Sudo et al. 2004).

Interestingly, these data are not consistent with other studies. The data suggest that the relative abundance of Lactobacillaceae is significantly higher in the gastrointestinal tract of people with schizophrenia. In addition, symptom severity and the presence of positive symptoms are positively correlated with the amount of Lactobacillus in the microbiome (Borkent et al. 2022).

One species that also affects dopamine metabolism is Clostridium, which is found in increased abundance in the microbiota of schizophrenic patients. Metabolites produced by Clostridia inhibit the activity of dopamine β-hydroxylase, an enzyme responsible for converting dopamine to norepinephrine. This leads to an increase in dopamine levels and a concomitant decrease in norepinephrine levels. Excess dopamine metabolites are an unfavorable situation because they can accumulate in the cytoplasm of neurons, resulting in oxidative damage. As a result, the oxidative stress caused by this process leads to a number of deleterious consequences, including apoptosis of dopaminergic neurons (Hamamah et al. 2022).

3.4.4. Short-chain fatty acids (SCFAs)

Although SCFAs are merely byproducts of the gut microbiota, they deserve special attention in the context of schizophrenia. In a study by Erny et al. (2015), SCFAs were administered to GF mice that had previously been shown to have microglia deformities caused by eradication of the gut microbiota. The results of the study indicate that microglia defects are reversible and can be restored by reintroducing viable complex microbiota or its metabolites, such as SCFAs (Erny et al. 2015).

The group of SCFAs includes such compounds as acetate, propionate, butyrate, pentanoic (valerian) acid and hexanoic (caproic) acid. They are products of fermentation of dietary fiber and starch by bacteria residing in the intestines (Tan et al. 2014).

Specific enzymes produced by different groups of bacteria are required to produce individual SCFAs. For example, acetate has its own characteristic production pathway – the Wood–Ljungdahl pathway, which is made possible by the presence of bacteria of the Firmicutes type (Ragsdale and Pierce 2008), while butyrate is most commonly produced by the Cytophaga and Flavobacterium groups of bacteria belonging to the Bacteroidetes type (Guilloteau et al. 2010). In addition, butyrate is known to increase the production of BDNF, which, through communication through the vagus nerve, results in increased neurotransmitter production (Round and Mazmanian 2009).

From studies conducted on mice that have been subjected to psychosocial stress, SCFA administration reduces the expression of genes in the hypothalamus involved in stress signaling. This results in a reduction in the stress response, anhedonia and stress-induced increase in intestinal permeability (van de Wouw et al. 2018).

These short-chain fatty acids have many health benefits, including anti-inflammatory effects, support of intestinal barrier function and regulation of energy metabolism (Morrison and Preston 2016). SCFAs can affect the function of distant cells in the body through activation of free fatty acid 2 (FFAR 2) and free fatty acid 3 (FFAR 3) receptors. These are expressed on the surface of various cells, including enteroendocrine cells and immune cells. Activation of these receptors by SCFAs affects a number of biological processes, including the immune and endocrine systems. SCFAs can affect immune cells responsible for inflammation, such as macrophages. Activation of the FFAR2 receptor activates a cascade of anti-inflammatory responses that are important in diseases where inflammation plays a potential role (Le Poul et al. 2003).

3.4.5. SCFAs and the blood-brain barrier

SCFAs have the ability to cross the blood-brain barrier, which gives them the ability to modulate microglia function and pro-inflammatory cytokines (Erny et al. 2015). A study by Braniste et al. (2014) reported that GF mice showed increased BBB permeability and this was associated with decreased expression of the tight junction proteins occludin and claudin-5, which are known to regulate barrier function in endothelial tissues. Subsequently, these GF mice were then monocolonized in the gut by C. tyrobutyricum, a bacterial strain that produces butyrate, or B. thetaiotaomicron, which produces mainly acetate and propionate. This was followed by a decrease in BBB permeability (Braniste et al. 2014).

Microglia function as tissue macrophages in the CNS. Highlighting the link between the gut microbiota and microglia is important because it has a direct impact on CNS function. Studies in GF mice have shown global defects in microglia. The complex gut microbiota supports the maintenance of microglia under stationary conditions, and its absence leads to defects in microglia maturation and function. The microbiota controls the innate immune function of microglia, preparing the brain for a rapid immune response in the face of pathogens. Impaired microglia function has been observed in mice lacking the microbiota and treated with antibiotics (Erny et al. 2015).

The pathophysiological cause of schizophrenia has been traced to neuroinflammation. Patients with schizophrenia have been shown to have elevated levels of pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α), in the cerebrospinal fluid. These cytokines are involved in neuronal damage reactions and microglia activation, leading to neurodegeneration. Activated microglia release cytokines, which may contribute to disease progression. By inference, abnormalities in microglia activation and the production of pro-inflammatory cytokines may play a key role in the pathogenesis of schizophrenia and other psychiatric disorders (Hong et al. 2016).

3.4.6. Tryptophan

Tryptophan is an essential amino acid and a precursor to many biologically active substances. In the context of mental health, its most important function is as a substrate for the production of the neurotransmitter serotonin. In many psychiatric and gastrointestinal diseases, increasing evidence points to dysregulation of the kynurenine pathway in tryptophan metabolism. The kynurenine pathway accounts for more than 95% of available peripheral tryptophan in

mammals (Platten et al. 2019). Changes in the gut microbiota, likely play a very important role in increased intestinal permeability and chronic inflammation in the body (Anmella et al. 2023). The kynurenine pathway is a complex process that requires the right conditions for all processes to take place properly. The key rate-limiting step in this metabolic cascade is catalyzed by indoleamine-2,3-dioxygenase or hepatic tryptophan 2,3-dioxygenase. The activity of both enzymes can be induced by inflammatory mediators and corticosteroids (Cryan and Dinan 2012).

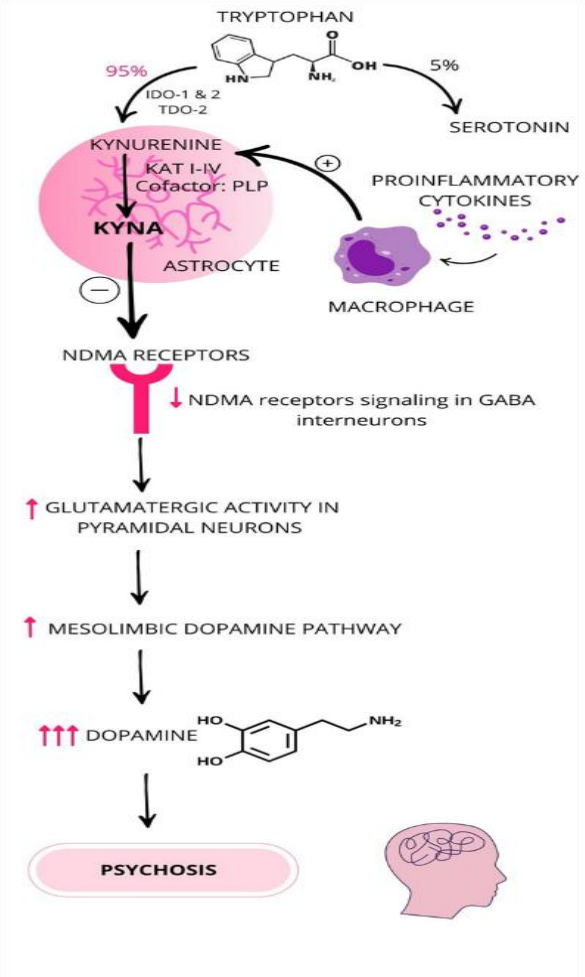
Feng Zhu et al. conducted a study to test whether transplanting fecal microbiota from schizophrenia patients not treated with drugs into mice free of certain pathogens can cause schizophrenia-like behavioral disorders. It has been shown that antibiotic-treated mice that received fecal microbiota transplants began to have behavioral disorders—psychomotor hyperactivity, learning and memory impairment. Also associated with the aforementioned disorders was increased degradation of tryptophan to kynurenic acid via the kynurenine pathway, as well as decreased biosynthesis of tryptophan itself (Zhu et al. 2019).

A study by Yusr I. Kazem et al. aimed to assess what effect supplementation with Bifidobacterium spp. has on improving mood and well-being and their correlation with blood kynurenine levels in healthy adult volunteers. Such an intervention has been shown to be important for well-being and to cause a significant decrease in blood kynurenine levels. There was also a significant increase in the number of Bifidobacterium in feces and a significant improvement in hemoglobin levels and liver enzyme activity (Kazem et al. 2021).

An in-depth analysis of the association of kynurenine metabolism with pro-inflammatory cytokines and its effects on attention and prefrontal cortex volume in schizophrenia was conducted by Jochen Kindler et al. It is known that the kynurenine metabolite (KYNA), derived from the kynurenine pathway, is elevated in the brains of people with schizophrenia. This study examined the extent to which: mRNA of kynurenine pathway enzymes in the brain, kynurenine metabolites in the brain, and kynurenine metabolites in plasma differed in the context of elevated cytokines in patients with schizophrenia compared to control groups (Kindler et al. 2019).

Kindler et al. analyzed the relationship between plasma kynurenine metabolites and cognitive function and brain volume in patients with elevated peripheral cytokine levels. Enzyme mRNA and metabolites were examined in two independent postmortem brain samples from a total of 71 patients with schizophrenia and 72 controls. Based on the results, Kindler and colleagues proposed a model of kynurenine pathway disruption in schizophrenia. According to this model, inflammatory mechanisms lead to increased conversion of tryptophan to kynurenine in the

periphery, which can cross the blood–brain barrier. In the brain, kynurenine is converted to kynurenic acid due to a pro-inflammatory increase in the activity of the enzyme kynurenine aminotransferase, which is associated with an increase in the mRNA of this enzyme in astroglia. Increased levels of kynurenic acid, according to this model, lead to brain volume loss and attention deficit disorder, mainly through blockade of N-methyl-D-aspartate receptors. Blockade of these receptors is a known trigger for the psychotic symptoms and cognitive deficits characteristic of schizophrenia (Kindler et al. 2019).



Scheme 2. KYNA synthesis and its impact on the pathogenesis of schizophrenia.

The starting point of the kynurenine pathway is tryptophan. About 95% of tryptophan is converted to kynurenine by the enzymes IDO (indoleamine 2,3-dioxygenase) and TDO (tryptophan 2,3-dioxygenase). IDO is induced by pro-inflammatory cytokines such as interferon-gamma (IFN-γ) and TNF-α, highlighting the importance of inflammation in activating the pathway. TDO, activated by glucocorticosteroids, acts mainly in the liver. Pro-

inflammatory cytokines stimulate macrophages to produce kynurenine. These cells have a key role in its production through the expression of the enzyme IDO-1. Astrocytes then convert this kynurenine to kynurenic acid (KYNA) with the involvement of kynurenine aminotransferase (KAT). High levels of KYNA can lead to NMDA receptor hypofunction, particularly in GABAergic interneurons, resulting in excessive glutamatergic activity in pyramidal neurons and increased stimulation of the mesolimbic pathway. There is an excessive release of dopamine especially in the ventral striatum. Increased dopaminergic activity is associated with positive symptoms of schizophrenia, such as hallucinations (Schwarcz et al. 2012).

4. Discussion

Research shows that microbial dysbiosis contributes to neurochemical imbalances and neuroinflammation, both of which exacerbate schizophrenic pathology. The reviewed literature emphasizes the gut–brain axis as a central player in the pathogenesis of schizophrenia, particularly through its effects on neurotransmitter synthesis and inflammatory regulation. Importantly, physical activity—especially aerobic exercise—has been shown to positively influence gut microbiota composition, reduce systemic inflammation, and enhance neuroplasticity. These physiological benefits align closely with the mechanisms disrupted in schizophrenia. Consequently, these discoveries call for deeper investigation into how the gut–brain axis interacts with neurotransmitter systems and how modifiable lifestyle factors such as exercise may serve as accessible, adjunctive interventions to help restore neurochemical balance and improve clinical outcomes in schizophrenia.

5. Conclusion

The literature reviewed underscores the pivotal role of the gut–brain axis in the pathogenesis of schizophrenia, particularly through its influence on neurotransmitter production and inflammatory regulation. Evidence indicates that microbial dysbiosis contributes to neurochemical imbalances and neuroinflammation, which exacerbate cognitive and affective symptoms in schizophrenia. Importantly, exercise therapy has emerged as a non-pharmacological intervention capable of modulating gut microbiota composition, enhancing hippocampal plasticity, and improving cognitive function. These findings support a multidimensional approach to schizophrenia treatment—one that integrates gut–brain axis modulation and structured physical activity as complementary strategies to traditional pharmacotherapy.

Disclosure

Author's contribution**:**

Conceptualization: [IZ], [WW]

Methodology: [PN], [KW], [JB], [JM]

Check: [JM], [IZ], [KW], [PN]

Investigation: [WW], [JB], [IZ]

Data curation: [KW], [PN], [IZ], [JM]

Writing – rough preparation: [JB], [WW], [PN]

Writing – review and editing: [IZ], [KW]

Visualization: [JM], [JB], [WW]

Project administration: [PN], [IZ], [KW]

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Conflict Of Interest

The authors declare no conflict of interest.
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