Review Article

Investigation of the Effects of the Gut-Brain Axis on Brain and Mental Health

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Abstract

There is a bidirectional and continuous relationship and communication between the brain and the gut. The gut-brain axis communicates not only through the microbiota but also via the autonomic nervous system. Microorganisms in the gut microbiota are known to contribute to the production of certain neurotransmitters that play roles in brain function, which may, in turn, influence mental health. Through this interaction, the gut microbiota and gastrointestinal system components play significant roles in human health. A healthy functioning of the gut-brain axis is essential for supporting the immune system, regulating mood, and maintaining cognitive and immune health. Recent studies highlight a connection and causality between the gut-brain-microbiota axis and neurological disorders such as Parkinson's disease, Alzheimer's disease, multiple sclerosis, and autism spectrum disorder, as well as psychiatric disorders like depression, anxiety, schizophrenia, and bipolar disorder. This paper reviews the impact of the gut-brain-microbiota axis on brain and mental health, emotion-thought-behavior systems, and its effects on neurological and psychiatric disorders.

Keywords: Gut-brain axis, microbiota, psychiatric disorders, neurological disorders

Introduction

In the human body, the gut is the largest digestive, immune and endocrine organ and has a nervous system that is relatively independent of the brain but is in constant communication with it, this nervous system is called the enteric nervous system[1]. The enteric nervous system plays an important role in the communication between the brain and the gut. The brain-gut axis is defined as a system that provides bidirectional communication between the autonomic nervous system and the enteric nervous system[2]. This communication is provided bidirectionally from top to bottom and bottom to top via vagus, sympathetic and spinal nerves, hormonal and neural pathways[3]. Recent studies have also shown that another factor that plays an important role in gut-brain communication is the gut microbiota. Gut microbiota is a term used to describe the microorganisms found in the gut ecosystem [4]. In recent studies, it has been explained that the microbiota-gut and brain axis is important in regulating physiological functions and that disorders in this axis play a role in the emergence of some diseases[5].

Neurological and psychiatric disorders cause significant disruptions and difficulties in fulfilling social roles and maintaining daily functioning. Emotional, cognitive and communicative difficulties are quite evident in psychotic disorders, mood disorders and autism spectrum disorders, and the treatment process is very important to overcome these difficulties[6]. Understanding the etiologic causes of these disorders has an important place in the treatment and prevention of these disorders. Understanding the effect of gut microbiota and gut-brain axis on the etiological causes of diseases is important for the effective use of regulations and treatments to be provided here. In this review, it is aimed to explain the effects of the brain- gut axis on brain and mental health and pathological interactions.

1. Brain-Gut-Microbiota Axis

The communication channels in the gut-brain axis can be summarized as four pathways from the gut to the brain and two pathways from the brain to the gut. Messages from the gut to the brain are transmitted via microbiota factors, gut hormones, neuropeptides and sensory neurons and cause an output in the brain. Messages from the brain to the gut are transmitted through autonomic and neuroendocrine pathways and cause an output in the gut[7].

The autonomic nervous system, one of the main components of the brain-gut axis, plays an important role in this communication through the vagus nerve and transmits 80% of the information carried from the gut to the brain [8]. In order to understand the role of the vagus nerve in the brain-gut axis, its relationship with neurotransmitters should also be evaluated. The enteric nervous system and the autonomic

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nervous system interact through neurotransmitters such as acetylcholine, adrenaline and noradrenaline, serotonin, dopamine, GABA, as well as through afferent and efferent neurons[5]. It is thought that the vagus nerve, which is sensitive to neurotransmitters, may also be effective on emotion regulation[9]. In this case, the vagus nerve is active both in the communication between the gut and the brain and in emotion regulation.

2. Hormones And Neurotransmitters In The Brain-Gut-Microbiota Axis

Neurotransmitters are molecules produced by the neuron and transmit between synapses. Neurotransmitters can be divided into two categories: excitatory (glutamate, acetylcholine, norepinephrine, dopamine) and sedative (GABA, serotonin) [10].

The gut microbiota can produce or support the production of neurotransmitters and metabolites such as GABA, histamine, acetylcholine and short-chain fatty acids. It is known that 90% of serotonin, a neurotransmitter that significantly supports mood well-being, is produced in the intestines [9]. It is considered that the imbalance of serotonin produced in the intestines may be associated with depression and anxiety[11].

Another neurotransmitter that the gut microbiota is thought to support the production of is dopamine. The production of dopamine, which is linked to reward and motivation, may contribute to mood well-being when supported by a healthy gut microbiota[12].

GABA is one of the most abundant sedatives in the brain and is also one of the neurotransmitters with muscle relaxant properties in the body[10]. Some studies have shown that some probiotic regulations in the gut microbiota play a role in GABA production and this regulation has been shown to change brain neurochemistry and at the same time, this change has been shown to reduce stress and depression-related behaviors[13].

Cortisol is known as the primary stress hormone affecting the brain and other organs. The hypothalamic-pituitary-adrenal (HPA) system is active and coordinates the production of cortisol[11]. A study shows that there is a direct link between the microbiota and the HPA axis, as well as a direct effect of the microbiota on the neurological activation of stress circuits[11].

The enteric nervous system is involved in the regulation of gut physiology through sensory neurons, motor neurons and interneurons. Recent evaluations show that neuropeptides are one of the important information carriers in the gut-brain interaction and that neuropeptides carry information from the gut to the brain[5]. Neuropeptides are small proteinaceous substances that are released, synthesized and used by neurons[14]. Information from the intestines is transmitted to the subcortical regions of the brain; this information is integrated with other information from the body and contextual information from the environment and can reach the level of consciousness and cause nausea, pain and discomfort. At the same time, changes in the intestine due to the information received from the brain can cause gastrointestinal dysfunction[7]. The reasons explained are important to understand the relationship between gastrointestinal disorders such as irritable bowel syndrome and psychiatric conditions such as anxiety, pain and depression.

3. Functions Of The Brain-Intestinal-Microbiota Axis

3.1 Protecting the Intestinal Barrier

The intestinal barrier is important in distinguishing between harmful and harmless bacteria and in supporting intestinal homeostasis. Dysregulated gut microbiota can cause both disruption of the integrity and permeability of the gut barrier and disruption of the integrity of the connection with the central nervous system [9]. The conditions that can be caused by intestinal permeability will be described in the section on pathological conditions.

3.2 Supporting the Immune System

The gut microbiota plays an important role in regulating the microbes and cells necessary for the development and healthy functioning of the immune system. There is thought to be a reciprocal relationship between immune cells and diversity in the gut microbiome[15]. Therefore, it can be said that a regulated gut microbiota is needed for the immune system to function. At the same time, during infancy when the immune system develops, gut microbiota is also effective in shaping immune tolerance[16].

3.3 Regulation of Mood and Behavior

The relationship between neurotransmitters that have an effect on mood and the brain-gut axis was explained above. The role of the brain-intestinal axis, which is especially active in the production and transportation of neurotransmitters such as serotonin, dopamine and GABA, which have an effect on mood, to the brain, is not limited to this.

Gut microbiota is thought to be associated with the stress response. Stress response can be defined as a change in physiological and neural states characterized by increased alertness[17]. It is known that the brain's perception of stress stimuli activates the 'survival mode' in the body and regulates appropriate responses. One of the active pathways in the regulation of this is known as the hypothalamic-pituitary-adrenal axis and it is accepted that this axis communicates with the brain-gut axis[9]. At the same time, while the perception of stress in the brain can cause dysregulation in the microbiota, a positive effect can be created in the microbiota order by providing stress management by the brain[17].

3.4 Gut Microbiota and Cognitive/Immune Health

Compositions in the gut microbiota are known to be associated with various mental disorders such as Alzheimer's, autism, depression and schizophrenia. Researcher Liu and colleagues[18], who wanted to see the potential for disruptions in the microbiota to significantly affect neurodevelopment and increase mental vulnerabilities, found that when the gut microbiome was altered with antibiotics in newborn mice, there were also changes in adult neurogenesis and behavioral impairment. This study shows that dysregulation of the gut microbiome disrupts neurodevelopment, increases anxiety, disrupts synaptic plasticity and impairs spatial memory. However, it is emphasized that regulation and therapeutic interventions in the microbiome also have an important role in the treatment of neurodevelopmental disorders[18]. At the same time, dysregulation in the microbiota is thought to cause neuroinflammation and neuronal impairments[19].

Disturbances in the microbiota also cause disturbances in the immune system and are thought to increase the risk of developing both metabolic syndromes (obesity, diabetes, insulin resistance, increased inflammation, liver diseases), and central nervous system diseases (cognitive and emotional disorders, pain modulation) and cardiovascular diseases[20].

4. Cerebrointestinal And Neurological Diseases

4.1 Parkinson's

Parkinson's disease is one of the most common neurodegenerative disorders associated with aging[21]. Parkinson's is classically characterized by tremor, bradykinesia, immobility or stiffness, slowness in the ability to express emotions, slowness in speech, symptoms of lack of harmony in voice and rhythm, difficulty in motor skills and coordination skills[22]. Prevalence studies have reported that this disease is observed in 1% of the population over the age of 65[23]. In a study conducted in Turkey, the prevalence was reported as 202/100.000[24]. When the etiology of Parkinson's disease is evaluated, it is stated that genetic factors, environmental factors and aging play a role in the etiology[23]. It is known to occur due to degeneration or cell loss in cells that secrete dopamine after substansia nigra damage in the brainstem region, but the exact cause of this damage is not known[23].

In a study conducted with 69 Parkinson's patients in order to understand genetic factors, differences were found in some gene groups and it was stated that these differences were significant for the etiology of the disease[25].

There are studies that try to evaluate environmental factors with the idea that genetic factors alone are not sufficient to explain the etiology. In one of the studies, it was stated that some genotype characteristics increase the risk of the disease and that pesticide exposure and smoking are effective on the age of onset of the disease[26]. In another similar study, it was reported that prenatal and postnatal exposure to environmental factors, especially heavy metals such as lead, mercury, aluminum, cadmium, arsenic, and some pesticides, leads to susceptibility to neurodegenerative diseases[27].

There are studies conducted to reveal the connection and relationality between the development of Parkinson's disease and symptoms of the gastrointestinal system. In one of these study reports, constipation and defecation dysfunction were found to precede other motor symptoms in Parkinson's patients and were accepted as a prominent premotor gastrointestinal symptom of Parkinson's[28]. In this study by Cersosimo et al[28], gastrointestinal symptoms such as drooling, dysphagia, dry mouth, bloating were also reported to precede motor symptoms and the number of symptoms reported was significantly related to the duration of the disease.

Irregularities in the brain-gut-microbiota axis are thought to cause gastrointestinal system dysfunctions found in more than 80% of Parkinson's patients, supporting the hypothesis that the pathological process spreads from the gut to the brain. It is also thought that this condition may contribute significantly to the pathogenesis of Parkinson's disease[29].

4.2 Autism Spectrum Disorder

Autism spectrum disorder refers to a neurodevelopmental disorder characterized by social communication disorder, restricted interests and repetitive motor movements[30]. Regarding the etiology of autism, it is stated that genetic factors may be effective, but environmental factors are also important[31]. When genetic factors are evaluated; it is stated that there may be anomalies in some chromosomes, changes in some copy numbers in the genome and genetic syndromes caused by single gene mutations may be important[32].

At the same time, in a study examining the effect of prenatal and perinatal period characteristics; it is stated that individuals with autism have a history of more prenatal and perinatal difficulties (parental age and age difference between parents, presence of medical illness in the mother, threat of miscarriage, negative life experiences during pregnancy, difficult / cesarean delivery, incubator / intensive care history, etc.)[33]. When its prevalence is evaluated, it is reported to be 1/59 according to 2018 data from the United States of America[34].

Up to 90% of children with autism have comorbidity of gastrointestinal disorders; constipation, diarrhea, abdominal pain, vomiting, poor nutrition have been reported. It is thought that disorders in the gastrointestinal system are associated with microbiota dysregulation and this dysregulation may predict the severity of autistic behavior[35].

In a study by Finegold and colleagues[31], when the microbiota patterns and bacterial diversity of healthy individuals were compared with the microbiota patterns and diversity of individuals with autism; it was stated that there was significantly more diversity in the gut microbiota of individuals with autism. The increased microflora observed in children with autism may contain harmful types of bacteria that may contribute to the severity of autism symptoms[31]. In another similar study, it was evaluated that there are some bacterial species in the microbiota of children with autism that are not found in the microbiota of healthy children and that they may be effective on symptoms, and it was stated that symptoms may be alleviated when microflora is regulated[36].

Some studies have shown that when the bacteria in the microbiome of children with autism were regulated, both gastrointestinal symptoms and autism symptoms improved, but all children relapsed after the treatment was stopped[37].

4.3 Alzheimer

Alzheimer's disease is clinically characterized by progressive memory loss and impairment of cognitive abilities[38]. Considering the etiologic causes of Alzheimer's disease, genetic and environmental factors may be effective, but it is thought to be heterogeneous and rare. There are different studies evaluating the prevalence of Alzheimer's disease. It is stated that 36.5 million people in the world are suffered from dementia and the majority of them have Alzheimer's disease[39]. However, in a study conducted between 2000 and 2012, it was reported that the prevalence of Alzheimer's disease decreased by 24%[40].

Recent research suggests that the microbiota is linked to Alzheimer's disease and supports the view that it is active in the development and exacerbation of its pathogenesis[41]. Aging affects the brain both cellularly and functionally and may be associated with a decline in sensory, motor and cognitive functions.

This age range is also associated with marked changes in the microbiome and degeneration of the gastrointestinal tract.

Inflammation associated with microbiome dysregulation is also thought to exacerbate cognitive decline[42]. Increased intestinal permeability, which causes some microbes as well as gastrointestinal products to enter the circulation, as well as microbiota dysregulation and aging, may contribute to the pathogenesis of Alzheimer's disease. It also suggests that dysregulation of the gastrointestinal tract may compromise the blood-brain barrier integrity of microbiota products in the blood, and microbes[43].

There is no definitive cure for Alzheimer's disease and treatments aim to further preserve cognition and memory and delay dysfunction; a study by Bonfili et al[44] explains that this can be achieved to some extent by adjustments to the microbiota and positive effects on neuronal pathways.

4.5 Multiple Sclerosis

Multiple Sclerosis is a disease of the myelin sheath of the central nervous system and is a progressive and chronic disease clinically characterized by recurrent neurological dysfunctions[45]. When the etiologic causes of multiple sclerosis are considered, genetic and environmental factors are important, and inflammation and changes in immune cells are also thought to be effective[46]. When the prevalence in Turkey is evaluated; it is reported to be between 0.4-1 per 1000 young adults[47]. In another study, the prevalence of familial multiple sclerosis was reported to be 11.5%[48].

Another factor thought to influence the disease is the intestinal flora. Intestinal permeability may cause some unwanted bacteria and molecules to enter the bloodstream. This can lead to dysregulation of the microbiota and an increased risk of multiple sclerosis[49]. In a study conducted by Berer et al.[50], they stated that irregularities in the microbiome may cause an increased risk of disease not only due to bacterial compositions but also by affecting the metabolic health of the gastrointestinal system. In their study, they also observed that when microbiota samples taken from individuals with the disease were transferred to healthy mice, disease development accelerated in these mice. This observation shows that intestinal microbiota contributes to disease pathogenesis[50].

In another study, when the microbiota of healthy individuals and individuals with multiple sclerosis were compared, it was reported that there were differences in specific gut bacteria in the microbiota of individuals with the disease and that these may have effects that may exacerbate or maintain autoimmune disease symptoms[51].

As can be understood from the research findings, it can be said that intestinal microbiota and intestinal permeability as a result of the destruction of the brain-intestinal barrier have an effect on the development and progression of multiple sclerosis. In the treatment of this disease, as in Alzheimer's disease, it is important to slow the progression and manage the symptoms[46]. Considering the contribution of the intestinal microbiota to the pathogenesis of the disease, it is thought that regulations in the microbiota may have important effects on the treatment and potential prevention of multiple sclerosis[50].

4.6 Epilepsy

Epilepsy is a condition caused by sudden and excessive electrical discharges in brain cells. It is characterized by seizures, fainting and bruising. Despite clinical and scientific research, the etiology of epilepsy still remains unclear and is thought to be influenced by genetic and environmental factors. Treatment is limited and mostly aimed at reducing seizure symptoms[52]. When the prevalence of epilepsy is evaluated, it is reported to be 5-8 per 1000 in high-income countries and 10 per 1000 in low-income countries[53].

A better understanding of etiological causes is important in order to increase therapeutic efficacy, so some studies have investigated whether there is a link between gut microbiota and epilepsy. In a study conducted by Şafak et al. , it is stated that there are significant differences between the microbiota of healthy individuals and the microbiota of epilepsy patients[54].

Studies show that gut microbiota affects brain-gut responses in the progression of autoimmune diseases, and it is reported that the risk of epilepsy is higher in some autoimmune diseases compared to healthy individuals[52].

Considering the research results, microorganisms in the gastrointestinal tract can be considered as an important factor in preventing the development or severity of epilepsy.

5. Cerebrointestinal Dysfunction And Psychiatric Illnesses

5.1 Depression

Depression is a psychiatric disorder that negatively affects emotions, thoughts and behaviors and is clinically characterized by depressed mood, loss of interest and lack of enjoyment. Symptoms of the disease include sleep disturbance, loss of appetite, weight changes, impaired ability to think and focus, fatigue, and difficulties in psychosocial, academic, occupational and family functioning[55]. When the prevalence of depression is evaluated; it is stated that 13% of women and 8% of men have been depressed at any period in their lives[56]. In another study, it was reported that the annual prevalence of depression in Turkey is 10.1%, and when those with mild symptoms are included in the evaluation, the point prevalence is between 6-8%[57].

Although many studies have been conducted to determine the etiology of depression, it has not yet been fully explained. Biological, genetic and psychosocial causes are considered.

When twin studies, family and adoption studies are evaluated, it is reported that genetic factors have an effect on the etiology of depression (some chromosons are associated with depression), and postmortem studies show that epigenetic factors have an effect on the predisposition or development of depression[58]. Psychosocial factors are addressed and analyzed by many theories.

Some researchers state that neurobiological factors are effective in the development of depression. When neurobiological factors are considered in the etiology of depression; the effect of neurochemical factors (serotonin deficiency, decrease in dopamine level, deterioration in monoamines, etc.), the role of noradrenergic system (decrease in receptor sensitivity in neuronal pathways in the brain, etc.), the role of hormonal factors in the neuroendocrinological context (abnormality in thyroid, adrenal, prolactin hormones) are evaluated[59].

In order to understand the etiology of depression, recent studies have focused on the brain-gut-microbiota axis. It is considered

that the brain-gut axis, which is effective in the regulation of the serotonergic system , may play an important role in the development of depression. In a study conducted by Jiang and colleagues[60], the microbiota of depressed individuals and healthy individuals were compared and it was reported that there was a decrease in some bacterial species in the microbiota of depressed individuals compared to normal and an increase in some bacterial species compared to normal. It is thought that increased bacterial diversity may contribute to the development of mood disorder[61]. In a similar study conducted by Aizawa et al.[62], it was reported that some microbiota bacterial species (Bifidobacterium and Lactobacillus) were significantly lower in the microbiota of depressed patients compared to those in the control group and irritable bowel syndrome was more common in depressed patients compared to the control group.

It is also thought that there is a cyclical relationship between depression and the microbiota and that there is a feedback loop between depressive states and microbiota dysregulation; that is, depression can cause some irregularities in the microbiota, while microbiota dysregulation can cause depression[42].

Considering all these research results, it is understood that gut health and microbiota balance play an important role in depression. These results may offer a new way to treat depression and it is thought that regulating and balancing intestinal health may be a helpful factor in the treatment of depression.

Based on this idea, in a randomized controlled study conducted by Steenbergen et al.[63], in the group with low and moderate depressive symptoms who received probiotic supplementation, participants reported that they were less disturbed by aggressive and ruminative thoughts when they were in a sad mood during probiotic use. This result is very important when the possibility of ruminative thoughts turning mood fluctuations into depressive periods is considered[63]. In another similar study, in a group of normal volunteers taking probiotic supplements for 30 days, the effectiveness of probiotic supplementation on the psychological state caused by daily life events was evaluated and it was stated that it could have a beneficial effect on general depression symptoms[64]. When these results are evaluated, it can be considered that probiotics may offer a useful therapeutic effect as an adjunctive treatment in the treatment of depression.

5.2 Anxiety Disorders

Anxiety at a level that does not impair daily functioning can be a beneficial emotional state that can create motivation in individuals, and even moderate anxiety is considered necessary and normal to increase performance. However, pathological anxiety is clinically characterized by physiological symptoms such as trembling, palpitations, dry mouth, muscle tension, etc., which cause impairment in the daily functioning of the person[65]. Anxiety disorder is a condition in which the individual worries more than they should about the events and situations they encounter in daily life[56]. Anxiety disorders, which are mostly characterized by muscle tension and the display of alertness, caution and avoidant behaviors in preparation for a possible danger, are defined under separate headings in the fifth Diagnostic and Statistical Manual of Mental Disorders (DSM-5). Anxiety disorders, which are defined under the subheadings of generalized anxiety disorder, selective mutism, specific phobia, social anxiety disorder, panic disorder, agoraphobia, separation anxiety disorder, anxiety disorder caused by substance/drug, anxiety disorder due to another health condition, another defined anxiety disorder, and undefined anxiety disorder, are discussed in a general framework in this study. The average prevalence of all these disorders defined under anxiety disorders in DSM-5 is around 6-7%[56].

When we look at the etiology of anxiety disorders, genetic, neurobiological factors, past experiences and general medical conditions or substance use are thought to be related to anxiety[66].

Neurobiological factors include norepinephrine, serotonin and norendocrine abnormalities, hypothalamic-pituitary-adrenal axis abnormalities[67].

In the etiology of anxiety, conditions that may occur with the stimulation and triggering of the hypothalamic-pituitary-adrenal axis are examined. In a study conducted on animals exposed to early stress, it is stated that there are physiological changes in the functions of this axis in anxiety states. At the same time, it was concluded that this early stressor affects the gut microbiota and leads to an abnormal behavioral stress response in adulthood[68]. It may be thought that especially early life stress experiences cause differences in the hypothalamic-pituitary-adrenal axis system and this may contribute to the development of anxiety.

Recently, researchers investigating the etiology of anxiety have focused on the relationship between gut health, microbiome and anxiety. In a study examining the differences in the microbiome of patients with generalized anxiety disorder, it was reported that there were differences in the microbiota bacteria of the control group and the group with generalized anxiety disorder; these differences were positively correlated with the severity of anxiety. It is stated that some bacterial species that are increased in the microbiota of the group with generalized anxiety disorder cause inflammation and intestinal permeability and this may be a factor in anxiety[69].

In another study, the effect of gastrointestinal system hormones on the coping of animals exposed to early maternal separation stress in adolescence was investigated. They reported that animals experiencing maternal separation have an intestinal hormone (cholecystokine) that decreases when they are separated from their mothers and increases when they are reunited. Based on this, in their research, it was stated that in the treatment provided through this hormone, anxiety-like behaviors tended to decrease, just as in reunion with the mother[70].

In another article, it is stated that peptides released by intestinal cells may affect mental health and contribute to the development of anxiety, and it is also stated that there is a therapeutic effect that can be created through peptides in the treatment process[71].

Studies focusing on the relationship between the gut-brain axis and anxiety have also noted the effect of the stress response on intestinal barrier leakage and causing intestinal permeability. Gastrointestinal system irregularities are reported to be associated with anxiety behaviors[72].

Relapse rates after anxiety treatment are quite common. It is thought that therapeutic effects on the gut-brain-microbiota axis may also be effective in the treatment of anxiety. In a study addressing this issue, rebuilding healthy gut microbiota was found to be important in alleviating anxiety. It states the importance of evaluating the use of probiotics and prebiotics for

the regulation of gut microbiota, diet, as well as the therapeutic effects of fecal microbiota transplantation[73]. However, more detailed studies and those made with human groups are needed to understand their effectiveness.

5.3 Schizophrenia

Clinically, it presents with a cluster of signs and symptoms characterized by disturbances in thinking, perception and cognition, motor movement abnormalities, restricted emotional expression, communication difficulties and apathy[74].

Symptoms of schizophrenia are divided into two groups: positive and negative. In positive symptoms, excesses and distortions in ordinary functions, disturbances in the evaluation of reality are observed; delusions, hallucinations, speech and behavioral problems (strange, excessive, bizarre, stereotypical behaviors; peripheral, tangential, pressured speech), confusion in associations occur. In negative symptoms, there is a decrease in usual functions or loss of function ; allusion, decrease and blunting of emotional reactions, avolition, withdrawal from social relations and self-isolation, decrease in sexual interest and desire[74]. The prevalence of schizophrenia in our country is reported as 8.9 per 1000 people[75].

Although the etiology of schizophrenia has not been fully determined, it is explained by genetic factors, environmental factors, effects caused by brain disorders, neurochemical factors and stress-diathesis model[76].

Studies conducted to understand genetic factors focus on twin studies and the presence of genes that have effects on chromosome regions. In twin studies, it is stated that schizophrenia is genetically transmitted, although it is not known exactly how it is transmitted, and that the risk rate is 8-10% if first-degree relatives have schizophrenia, 13-14% if one of the parents has schizophrenia, and the risk rate increases up to 50% when both parents have schizophrenia[77]. Chromosome studies have shown that the presence of certain chromosomes is effective in the development of schizophrenia, and the risk of developing the disease increases in the presence of at least two genes affecting dopamine 3 and serotonin 2A receptors[76]. Although these genes and chromosomes are thought to be effective in the development of the disease, the exact mechanism of action has not yet been clarified.

When environmental factors are evaluated; in a meta-analysis study focused on complications experienced during pregnancy and childbirth, it is stated that pregnancy complications (bleeding, diabetes, rhesus incompatibility, etc.), abnormal fetal growth (low birth weight, small head circumference etc.), birth complications (asphyxia, uterine atony, emergency cesarean section, etc.) can be effective in the development of schizophrenia[78]. Other environmental factors include infections (rubella, influenza, etc.), cannabis use, childhood traumas and socioeconomic status[79].

When the interaction between brain disruptions and schizophrenia is examined; neurodevelopmental and neurodegenerative processes are taken into consideration. In neurodevelopmental studies, it is suggested that synaptic pruning above a certain level may initiate schizophrenia, and as another factor, it is stated that the absence of gliosis in individuals with schizophrenia may be effective[76]. The fact that late diagnosis or prolonged absence of treatment worsens the prognosis of schizophrenia and that disability loss in patients who do not receive treatment is higher and faster than in patients who receive regular treatment suggests that the disease also has a neurodegenerative aspect[76].

Research examining the impact of biochemical processes in the brain on schizophrenia focuses on the effects of neurotransmitters in the brain. For example, studies focusing on the effect of dopamine are frequently found and it is stated that dopamine excess plays an important role in the etiology of schizophrenia because psychostimulants that increase dopamine activity cause schizophrenia-like effects and blocking dopamine receptors reduces symptoms[74]. Research has also focused on serotonin, norepinephrine, glutamate, GABA, acetylcholine neurotransmitters.

It is accepted that microbial agents in the gut microbiota are involved in the etiology of many diseases, and although it is thought to be effective in schizophrenia, it cannot be attributed to a single microbial agent. However, in a study conducted by Castro-Nallar et al.[80] on the oropharyngeal microbiome with a control group, it was reported that there were significant differences in both microbial bacterial genera and bacterial ratios in schizophrenia patients compared to healthy individuals in the control group. It is stated that the microbiota of schizophrenia patients are less rich in terms of species, but there is a particular increase in some bacterial species (Ascomycota) and at the same time, different types of bacteria (Lactobacilli, Bifidobacterium) are abundant[80].

NDMA receptor hypofunction is known to be important in the development of schizophrenia, as NDMA receptor antagonists produce schizophrenia-like symptoms, while agents that increase receptor function reduce negative symptoms[81]. It is also stated in studies that the microbiome should be in normal order for NDMA receptors to function properly[81].

At the same time, it has been reported that damage to the gastrointestinal tract can also lead to the disease; in studies examining markers of intestinal inflammation and bacterial translocation, structural damage to the gastrointestinal tract barrier has been reported in schizophrenia patients[81].

The treatment of schizophrenia primarily aims to reduce symptoms, reduce disability and improve the patient's adaptation skills. Pharmacological treatment, therapy and psychosocial treatments, and in some cases electro-convulsive therapy (ECT) are used. A better understanding of the etiology is important to increase treatment options. Although the mechanism of action of the gastrointestinal system and gut microbiota in the etiology of schizophrenia has not yet been clarified, some therapeutic interventions can be provided through the microbiota. It can be stated that understanding the mechanism of action is important for the use of interventions that can regulate the gastrointestinal system and microbiota balance such as anti-inflammatory treatments, the use of probiotics and prebiotics, intervention in digestive enzymes and diet in the treatment of schizophrenia[82].

A common therapeutic effect stated by many studies comes from the dietary mechanism. It is stated that there are solutions in schizophrenia symptoms with gluten-free, dairy-free, grain-free diet arrangements, but it is also added that more data is needed[81].

5.4 Bipolar Disorder

Bipolar disorder is characterized by progressive mood swings with manic and depressive phases. It is characterized by chronically occurring episodes of mania or hypomania alternating with depression[83]. Bipolar disorder is divided into two categories, type I and type II. Type I bipolar disorder is characterized by manic episodes, while type II bipolar disorder is characterized by hypomanic episodes and recurrent depressive episodes[84]. In a study conducted in the city center of Izmir, where the prevalence rate of bipolar disorder was evaluated, it was reported that the prevalence rate for bipolar disorder I was 0.37%[85].

Although the etiology of bipolar disorder cannot be fully explained, a combination of environmental, genetic and psychosocial factors seems to be important. Some of the studies evaluating genetic factors refer to DNA markers related to chromosome 11. Research has established an association between 30 genes and an increased risk of the disease state[83]. At the same time, twin studies indicate that bipolar disorder may be hereditary, and that the risk of the disease is four times higher in children whose parents have bipolar disorder than in children with healthy parents[86].

Studies focusing on neurotransmitter dysregulation have found norepinephrine, dopamine and serotonin dysregulation to be particularly important[86]. In a large-scale meta-analysis study conducted to examine the changes and disruptions in the brain in bipolar disorder; neuroimaging examinations have shown lower cortical thickness, smaller subcortical volume and impaired white matter integrity associated with bipolar disorder[87].

Although it has been associated with challenging life events, childhood maltreatment, emotional abuse or neglect as environmental factors, a complete causality cannot be established[83].

There are also studies focusing on the gut microbiome and gastrointestinal dysregulation in investigating the etiology of bipolar disorder. A study analyzing fecal microbiome samples from healthy individuals and individuals diagnosed with bipolar disorder found significant differences between the microbiome communities of the two groups. For example some bacterial species (Faecalibacterium) were found to be reduced in the microbiome of bipolar patients and it was evaluated that increasing this bacterium in the microbiota may have a therapeutic effect[88]. In a study conducted by McIntyre and colleagues[89], when the microbiota samples of the group diagnosed with bipolar disorder and healthy individuals were compared, it was stated that the microbiota diversity of the group with bipolar disorder was less and at the same time some bacterial species (Clostridiaceae and Collinsella) were more abundant.

There are also studies addressing the causality of inflammation in bipolar disorder. In one of the studies, it was stated that there were significant improvements in mania symptoms within 15 days after normalization of inflammatory markers[90].

It has been reported that there are neurometabolite pathways through which the microbiota of the gastrointestinal tract affect the brain and behavior (e.g. GABA is produced by lactobacillus, bifidobacterium, while dopamine can be produced by bacillus and serratia) and that neurotransmitters produced there may play a role in bipolar disorder[90].

In the treatment of bipolar disorder, treatment is tried to be applied at three symptom levels: manic symptoms, mixed episodes and depression. While it is important to resolve the developed episode in acute treatment, it is considered important to delay the development of attacks, reduce the severity of the attacks that occur and reduce the severity of symptoms between attacks in maintenance treatment[86]. Pharmacotherapy is considered very important in the treatment of bipolar disorder. In addition, non-pharmacological, psychosocial interventions, cognitive-behavioral therapy, electro-convulsive therapy, dietary and probiotic treatments are significantly researched and attracted attention[91].

Obi-Azuike et al[92] reported that probiotic supplementation significantly improved depressive symptoms and cognitive impairment and reduced rehospitalization of patients diagnosed with bipolar disorder. In another similar study, 66 patients hospitalized for mania were divided into two groups as control and experimental groups. The control group was given placebo, while the experimental group was given probiotic supplements and followed for 24 weeks. It is stated that 24 of 33 individuals receiving placebo were re-hospitalized, while 8 of 33 individuals receiving probiotics were re-hospitalized[93]. The aforementioned research results suggest that providing an order in the gut microbiota through probiotics may have a therapeutic effect on the symptoms of bipolar disorder, but more evidence-based data are needed.

Another method used to directly manipulate the gut microbiota is fecal microbiota transplantation. According to one study, fecal microbiota transplantation can have a therapeutic effect in patients with bipolar disorder. It has been observed that a woman diagnosed with bipolar disorder undergoing at least nine fecal microbiota transplants from her healthy husband improved her manic and depressive symptoms in six months[94].

The relationship and causality between bipolar disorder and dysregulation of the gastrointestinal tract and gut microbiota needs further investigation. It is thought that therapeutic effects on the gut microbiome may have therapeutic effects on bipolar disorder, but more evidence-based data are needed.

Conclusion

Gastrointestinal system elements and gut microbiota are thought to affect mental and brain health, emotion-thought-behavior systems through the brain-gut axis. Today, the etiology and treatment modalities of psychiatric and neurological diseases have gained great importance. It is very important to understand the effects of the brain-gut axis on body-brain-spirit health in order to develop new ways of treatment. Considering the effects of the brain-intestinal axis, it seems that it will be the subject of new research in neuroscience in the coming years. More research is needed to utilize the therapeutic effects of these microorganisms in the treatment of neurological and psychiatric disorders. Pharmacological treatments that can provide these therapeutic effects are called psychobiotics[95] and psychomicrobiotics[96] and are already being used and researched. However, further evidence-based studies are recommended to understand the mechanisms of therapeutic effects that the brain-gut-microbiota axis may provide.

Patient informed consent

There is no need for patient informed consent.

Ethics committee approval

There is no need for ethics committee approval.

Conflict of interest

There is no conflict of interest to declare.

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Author contribution subject and rate

- Feride Nihal Balcı (%100) Design the research, data collection and wrote the whole manuscript.

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