Review

Psikiyatride Güncel Yaklaşımlar-Current Approaches in Psychiatry 2022; 14(4):446-459

DOI: 10.18863/pgy.1034963

Cognitive, Emotional, Behavioral and Physiological Evaluation of the Relationship Between Brain and Gut Microbiota

Beyin ve Bağırsak Mikrobiyotası Arasındaki İlişkinin Bilişsel, Duygusal, Davranışsal ve Fizyolojik Açıdan Değerlendirilmesi

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ABSTRACT

The aim of this study is to examine the effect of gut microbiota on brain functions, mood and psychiatric disorders such as depression, anxiety and behavioral addictions, neurotransmitter levels, cognitive processes such as self-control, decision making and delayed gratification. In this context, the relevant literature was reviewed and the findings were evaluated. The relationships of the bidirectional communication between the brain-gut axis with cognitive, emotional, behavioral and physiological processes were explained with a diagram. As a result, although more research is needed on this subject, it has been observed that the brain-gut axis is bidirectionally established through neural, stress, endocrine and immune systems. In this bidirectional communication process, there are interactions in the context of cognitive, emotional, behavioral and other physiological factors. These factors both individually enter into bidirectional relationships with the brain and gut microbiota and are affected by the bidirectional communication between the brain and gut.

Key words: Gut, brain, microbiota, HPA, behavior, cognition, mood

ÖZ

Bu araştırmanın amacı, bağırsak mikrobiyotasının; beyin fonksiyonlarında, depresyon, kaygı ve davranışsal bağımlılıklar gibi duygu durum ve psikiyatrik bozukluklarda, nörotransmiter düzeylerinde, özkontrol, karar verme ve haz erteleme gibi bilişsel süreçlerdeki etkisini incelemektir. Bu bağlamda ilgili literatür taranmış ve bulgular değerlendirilmiştir. Literatür incelemeleri sonucu ulaşılan beyin-bağırsak ekseni arasındaki çift yönlü iletişimin bilişsel, duygusal, davranışsal ve fizyolojik süreçlerle ilişkileri bir diyagram ile açıklanmıştır. Sonuç olarak, bu konuda daha çok araştırmaya ihtiyaç olunmasına karşın, beyin-bağırsak ekseninin nöral, stres, endokrin ve bağışıklık sistemleri üzerinden çift yönlü olarak kurulduğu görülmüştür. Bu çift yönlü iletişim sürecinde bilişsel, duygusal, davranışsal ve diğer fizyolojik faktörler bağlamında etkileşimler bulunmaktadır. Bu faktörlerin hem ayrı ayrı beyin ve bağırsak mikrobiyotasıyla çift yönlü ilişkilere girdiği hem de beyin-bağırsak arasındaki çift yönlü iletişimden etkilendiği sonucuna varılmıştır.

Anahtar sözcükler: Bağırsak, beyin, mikrobiyota, HPA, davranış, biliş, duygu durum

Introduction

Early life experiences, which start with the prenatal period and continue in the first years after birth, have important roles in the development and functions of people throughout their lives. Development continues rapidly in physical, cognitive, emotional, social and moral aspects, especially until the age of six. Although development is substantially complete during this period, various types of development continue throughout life. In this process, which begins in the prenatal period, the human adapts to the environment and experiences a rapid learning process. In this respect, s/he also gets acquainted with various forms of different microorganisms.

While the development of the brain continues on the one hand, the enteric nervous system, also known by many as the second brain, or more specifically as the gut microbiota begins to form its own flora. These two organs are interconnected. In this respect, it was claimed years ago that their development could affect each other, and various related studies began to be conducted. Bidirectional

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communication between the gastrointestinal (GI) system and the brain is regulated at both central and enteric nervous systems as well as at immunological levels. Therefore, problems in this system may cause disruptions or changes in behavior, particularly in the stress response (Cryan and O'Mahony 2011).

Unhealthy microbiota or impaired microbiome, which seriously damages the functionality of the individual and brings along various problems such as disordered eating, limitation in physical activity and sleep disorder, may have significant effects on cognition, emotions and behaviors in this regard (Benton et al. 2007, Blasco et al. 2017). It is important to eliminate the lack of data in order to understand the relationships and connections between them and to develop etiological studies for treatment. In the light of the data obtained, it is thought that the components of the gut microbiota are in a bidirectional relationship with behavioral disorders such as addiction and especially with problems accompanying sedentary life, eating disorders and irregular and unhealthy nutrition (Penders et al. 2006, Xu and Knight 2015, Skosnik and Cortes-Briones 2016, Özdemir and Büyüktuncer 2017).

The effects of gut microbiota on brain functions, brain chemistry, neural development and behavior have been investigated in recent years, especially in mice with and without microbes. Although transferring studies on animals to the human population and generalizing the findings to humans pose some problems, the results are actually exciting. In this respect, the focus was on the positive or negative effects of factors such as gut flora, probiotic agents, pathogenic infections and antibiotics in this bidirectional communication. Undoubtedly, other factors not known yet also play a role in the bidirectional communication between the brain and the gut.

Combinations of relationships between the central nervous system, the GI system, the gut, and stress constitute the basis of the functional communication process. Functional communication between the GI and central nervous system is bidirectional (Stasi et al. 2019) and includes anatomical connections such as the vagus nerve as well as humoral components including the immune system and the Hypothalamus-Pituitary-Adrenal (HPA) axis. Physical and psychological stress is known to affect not only the immune system but also hormonal and GI homeostasis (Bailey et al. 2011, O'Mahony et al. 2011, Gao et al. 2018). Immune and neuroendocrine systems provide integrated responses to environmental signals. The relationship between stress and immune function was demonstrated in many contexts, including the proliferative response to mitogens and the cellular activity. Stress conditions may lead to uncontrolled production of cytokines or an imbalance between pro-inflammatory and anti-inflammatory cytokines (Logan and Katzman 2005, Brenner and Chey 2009, Bailey et al. 2011). Irregularity of innate and adaptive gut immune responses to bacterial flora plays a role in a variety of pathogenetic mechanisms. Long-term psychological stress also results in a significant reduction in mucin production, leading to impairment of healthy gut flora by pathogenic organisms.

In this respect, the purpose of the study was to examine the effect of the gut microbiota on brain functions, on behavioral and psychiatric disorders such as depression, anxiety and addiction, on physiological processes such as neurotransmitter (serotonin, dopamine) levels as well as on cognitive processes of gratification procrastination, self-control and decision making. In this respect, in this study, the relevant literature, belonging especially to the last 20 years, was reviewed, and the interactions of the brain-gut axis with cognitive, emotional, behavioral and physiological processes were evaluated.

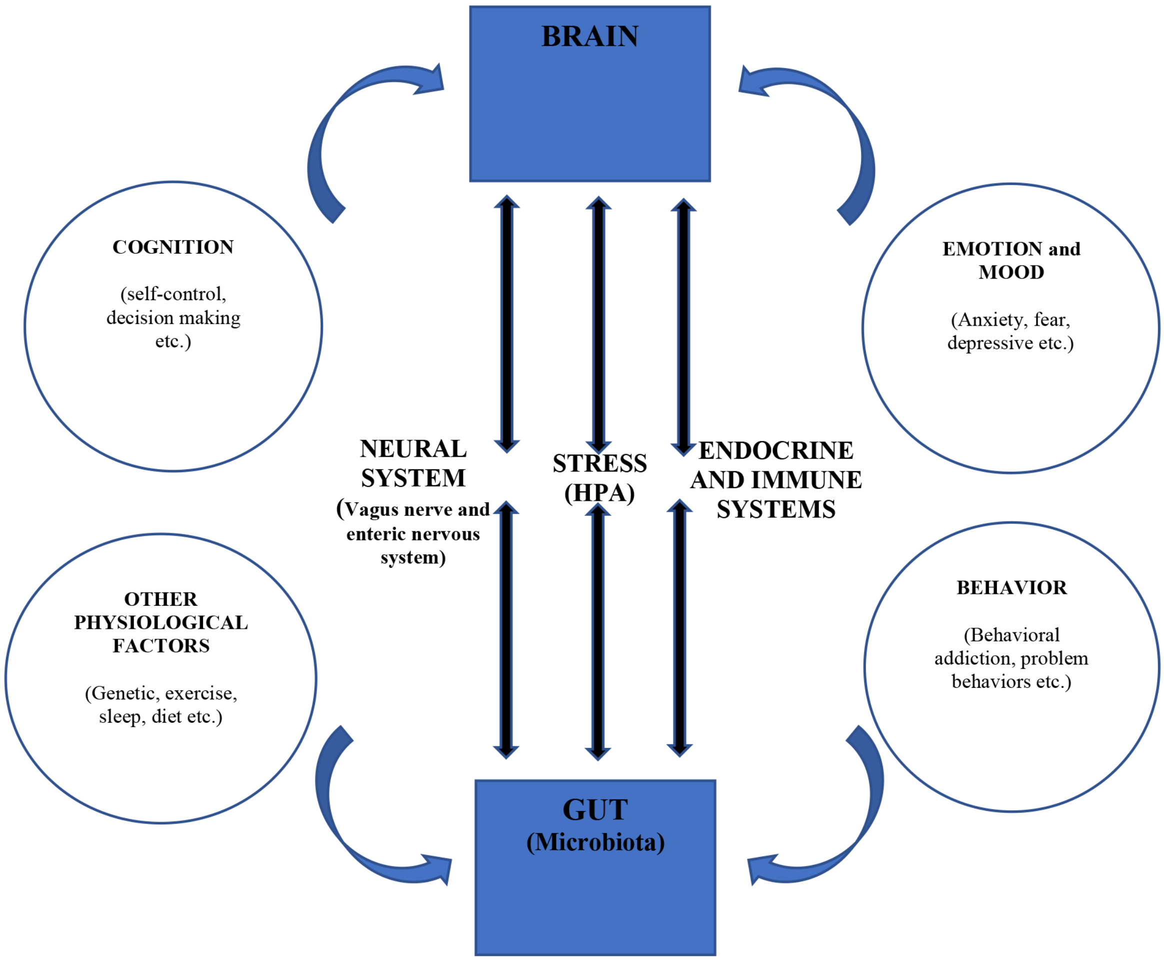
An Overview of the Brain-Gut Connection

In this study, as a result of the evaluations, the bidirectional communication between the brain-gut axis and the interactions of this axis with cognitive, emotional, behavioral and physiological processes are illustrated in Figure 1.

When Figure 1 is examined, it is seen that the brain-gut axis is established bidirectionally over the neural, stress, endocrine and immune systems. In this bidirectional communication process, there are interactions in the context of cognitive, emotional, behavioral and other physiological factors. These factors not only enter into bidirectional relationships separately with the brain and gut microbiota, but affected as well by the bidirectional communication between the brain and gut. Processes related to cognition, emotion and behavior also bring up the connection between the gut microbiota and the emergence of problems or disorders that constitute the basis of these processes in the brain. In other words, the connections between gut microbiota and cognition, emotion and behavior might include the problems and disorders related to these mechanisms in the process in the context of a cause-effect relationship. For example, gut microbiota influences cognitive processes, or cognitive processes influence gut microbiota. Similarly, depression damages the balance of the gut microbiota, or the gut microbiota facilitates depression or contributes to the prevention of depression.

Undoubtedly, separating and simplifying the diagram of connections presented in Figure 1 in a clear-cut manner would not be correct, even if it makes it easier for us to understand the process. In another saying, for instance, it would be wrong to evaluate the concept of behavioral addiction only within the scope of psychiatric disorders or behavioral dimensions (there are also cognitive, emotional, and other similar dimensions) and to evaluate the concept of impulsivity only in the behavioral dimension. At this point, not only the connections between the gut microbiota and these sample concepts to be discussed below in terms of the brain-gut connection but also the connections with each other or with different dimensions should be taken into consideration.

In addition to the seemingly complex connection between the gut microbiota and the brain, many arguments involved in the process have various effect mechanisms. For example, when evaluating the connections between the gut microbiota and the mood or psychiatric disorders, we cannot ignore cognitive processes, genetic factors and other factors such as sleep,



Şekil 1. Beyin-Bağırsak Bağlantısı

nutrition or exercise in this interaction. In general, cognition, emotion, and behavior are interconnected in different patterns. This situation is probably seen as well in the connection with the gut microbiota.

Gut Microbiota

Basically, gut bacteria regulate digestion and metabolism, programs the body's immune system, and builds and maintains the gut wall that protects the body from external invaders. Beneficial bacteria in the gut inhibit the establishment and reproduction of harmful microbes and produce anti-microbial chemicals that protect the host against pathogens (Carpenter 2012). Beneficial bacteria or probiotic bacteria in the gut are live but non-pathogenic microorganisms that normally live in the gut contributing to the health of the host by improving the microbial balance (Franco-Robles and López 2015).

The gut microbiota consists of 100 trillion microorganisms in total, with an independent neural network in which 100 million neurons weighing 2 kg (Thomas et al. 2015) are embedded in the gut wall (Putignani et al. 2014). The gut microbiota contains approximately 150 times more different genes than the human genome (Qin et al. 2010). The most common phyla in the small gut are *Firmicutes* and *Bacteroidetes*. *Proteobacteria, Actinobacteria, Fusobacteria, Archea* and *Verrucomicrobia* are present in smaller amounts (Grenham et al. 2011). It is accepted that approximately one-third of the gut microbiota is common in most people, while the other two-thirds are individual (Qin et al. 2010).

The gut microbiota *become relatively stable until 3 years of age* and lose its diversity in old age. The gold standard of microbiota in infants occurs as a result of vaginal delivery and breastfeeding (Salazar et al. 2014). It is known that specific bacterial strains are passed from mothers to their inftants during vaginal delivery and that microbial colonization differences are seen 3 days after birth in those born via cesarean delivery. In one study, it was shown that cesarean delivery impaired the transmission from mother to newborn of specific microbial strains involved in the preparation of the neonatal immune system (Wampach et al. 2018). It was reported that breast milk also shaped the gut microbiota and that there was an increase in the species composition number and number of bifidobacteria in breastfed infants compared to formula-fed infants (Solís et al. 2010).

The composition of the gut microbiota in terms of diversity and number of some bacterial species indicates a healthy gut. In addition, there is a balance in the composition of beneficial and disease-causing bacteria in the gut. A healthy gut cannot be mentioned when this balance is impaired in favor of bacteria that cause a disease.

Bacteria in our body, most of which are in our gut, are approximately 10 times more abundant than our own cells (Carpenter et al. 2012). The gut has a surprisingly complex neural network that can take advantage of this bacterial ecosystem for both physical and psychological well-being. Studies found that for example, changing the balance between beneficial and disease-causing bacteria in an animal's gut can alter brain chemistry and make it courageous or more anxious (Bravo et al. 2011, Carpenter et al. 2012). The brain can also have strong influence on gut bacteria. As many studies showed, even mild stress can impair the microbial balance in the gut, making the host more vulnerable to infectious diseases and triggering a series of molecular reactions that feed back into the central nervous system (O'Mahony et al. 2011, Carpenter et al. 2012).

Gut microbiota is shaped by such factors affecting natural immunity as exercise, sleep order, antibiotic use and diet (Penders et al. 2006). Moreover, it is argued that there is a cross-interaction between G-linked receptors expressed in the nervous system and innate immunity and *Caenorhabditis elegans* (Aballay 2009). It is known that diet types such as Western-style diet, Mediterranean-type diet, gluten-free diet affect the microbiota (Özdemir and Büyüktuncer 2017). For instance, high-fat and protein-rich diets result in significant reductions in bifidobacteria and butriate-producing bacteria, while a high-fat diet and fermentable fibers/ probiotics_have an opposite effect (Brown et.al. 2012, Özdemir and Büyüktuncer 2017). Diet activates the composition and metabolism of the gut microbiota, influencing the capacity of bacteria to produce microbial metabolites and allowing connections to be established between different physiological states (Koh et al. 2016). The gut microbiota responds very quickly and effectively to major dietary changes, such as switching from a plant-based diet to an animal-based diet or increasing the intake of dietary fiber (David et al. 2014). However, the most influential of all external factors affecting the gut microbiota is the general eating pattern (Xu and Knight 2015).

In some studies, it was seen that the short-term consumption of a diet consisting entirely of animal or vegetable products changed the structure of the microbiota. In addition, a strict animal diet was shown to increase the abundance of bile-tolerant microorganisms and to decrease the levels of *Firmicutes*, which metabolize dietary plant polysaccharides (David et al. 2014). In another study, enterotypes were strongly associated with long-term dietary habits (particularly, *Prevotella* in carbohydrate diets and *Bacteroides* in protein and animal-fat diets) (Wu et al. 2011). In one study, it was found that some bacterial groups increased within a few days with increased intake of resistant starch yet were equally rapidly reversed with diet switching. At the same time, as this interaction was not the same in every individual, it was thought that these changes depended on the *initial composition* of the individual's gut microbiota (Walker et al. 2011).

DNA damage was observed in colonic mucosal cells in diets low in fermented carbohydrates and rich in protein (especially red meat) (Conlon and Bird 2015). In addition, for the gut microbiota, vegetable proteins are more beneficial than animal proteins, and unsaturated fats are more beneficial than saturated fats (Singh et al. 2017). In one study, it was revealed that the whole-grain diet did not change the gut microbiota when compared to the refined grain diet (Roager et al. 2019). In one other study, it was observed that children from Burkina Faso (in the African continent) who followed a high-fiber diet based on plant sources had better microbiota (De Filippo et al. 2010).

A healthy microbiota is important in terms of the diversity and continuity of beneficial bacteria. The unhealthy microbiota in this respect indicates an imbalance in the microbiota. In addition, an unhealthy microbiota occurs either in relation to the diversity and number of bacteria, or as a result of external factors due to the use of certain drugs such as antibiotics. There are studies showing that antibiotics cause serious damage to the gut microbiota in older ages. A longitudinal study focusing on the relationship between antibiotics and microbiota showed that the changes caused especially in the *Bacteriodes* group by the use of antibiotics for a week did not return to their former state for a long time (Jernberg et al. 2007). In this respect, antibiotics may cause a decrease of 25% in microbial diversity shortly after their use (Panda et al. 2014). There are also studies showing that antibiotics cause serious damage to the gut microbiota in older ages (Panda et al. 2014). In some other studies, it was observed that most of the bacteria were severely affected by antibiotics and that only the *Akkermansia* type, the only representative of the *Verrucomicrobia* phylum, was not affected by any of the antibiotics (Zaura et al. 2015).

A number of studies revealed connections between gut microbiota, immune system and cytokine response. The gut microbiota is a crucial factor for shaping and modulating immune system responses associated with various autoimmune diseases (Kosiewicz et al. 2011). Changes in gut microbiome composition are also associated with abnormal immune responses and are often accompanied by abnormal inflammatory cytokine production (Paun et al. 2016, Schirmer et al. 2016). At the same time, cytokine profiles affected by altered gut microbiota in a neurodegenerative disease such as Parkinson may contribute to inflammatory processes of abnormal immune responses in the disease (Lin et al. 2019). The gut microbiota may also influence cytokines through gut permeability and therefore have effects on the brain. One of the most important biological indicators of gut permeability is zonulin. Zonulin affects gut permeability, and Claudin-5 affects blood brain barrier permeability. In some neuropsychiatric disorders, attention was drawn to the connections between psychiatric disorders and gut and blood-brain barrier permeability depending on the levels of zonulin and claudin-5 (Işık et al. 2020, Kılıç et al. 2020).

Connections Between Gut Microbiota and Nervous System

The enteric nervous system (Gershon 1999), which includes the gut and is also called the 'second brain' by some researchers, is a systematic neural network consisting of about 100 million neurons in the GI system, the control center of the gut (Buhner and Schemann 2012). Depending on the general eating pattern, the components of the gut microbiota affect the metabolism, chemistry and functions of the individual through the complex bidirectional communication network (microbiota-gut-brain axis) existing between the central nervous system and the GI system (Grenham et al. 2011, Zalar et al. 2018).

The key elements of the brain-gut axis are especially the neural and hormonal systems. The effects of the autonomic nervous system and HPA axis on food intake also seem to affect the gut microbiota composition (O'Mahony et al. 2011). One of these bidirectional connections occuring directly or indriectly between the nervous system and the gut microbiota could be the brain's influence on the components of the gut microbiota via the HPA axis under stress and could be the subsequent effects of the gut microbiota on brain functions (Duerkop et al. 2009, O'Mahony et al. 2011).

Although not all the effect mechanisms are known, it is claimed that the central nervous system and the gut microbiota have a bidirectional interaction with the autonomic, neuroendocrine and immune pathways and that gut microbiota could be effective on many psychiatric problems such as anxiety and mood disorders (Bravo et al. 2011, Rieder et al. 2017). This judgment was also proved in studies on germ-free mice and on those with germ, and it was revealed that the presence or absence of conventional gut microbiota affected behavioral development and had influence on neurochemical changes in the brain (Neufeld et al. 2010).

Modulation of transporters in the gut (e.g., serotonin, melatonin, histamines, and acetylcholine) is another possible effect mechanism that may mediate the effects of the gut microbiota (Heijtz et al. 2011). For instance, gut microbiota also regulates neuronal functions of the enteric nervous system. Some gut microbes directly affect synthesis of serotonin (5-HT). Serotonin is a neurotransmitter that has essential roles in basic brain function and regulation of GI function.

It could be stated that the relationship between gut and brain functions has not only direct effects but also indirect effects by disrupting the gut functions of some basic mechanisms, such as especially stress. From this point of view, it is seen that in the treatment of some psychiatric disorders such as depression, some treatments are, besides antidepressants, applied to eliminate gut-related problems, which contributes to the brain.

Connections Between the Gut Microbiota and Stress

Stress is regarded as a phenomenon or experience that threatens an individual's ability to adapt and cope with difficulties (Ferrari and Villa 2017). This situation can manifest itself with the reaction to an external stimulus that occurs during the fight or flight process defined by Cannon (1932), and it also includes internal stimuli. In other words, stress can also be defined as a psychological and behavioral response (Levine 1985). Selye (1936) defined stress within the scope of General Adaptation Syndrome and explained three stages of stress. When a threat or stressor is identified or recognized, the body goes into an "alarm" state (for example, adrenaline is released). If the stress continues, the organism enters the "resistance" stage, where it tries to cope by using stress protection and defense mechanisms. In the 'exhaustion' phase, the organism's resources are eventually depleted, and the organism cannot continue its normal function. In this case, long-term damage may occur as the capacity of the glands and the immune system are depleted, and diseases may manifest themselves. Selye (1936) also refers to persistent stresses which are not resolved through coping or adaptation, and which may lead to an illness such as escape (anxiety) or withdrawal (depression) behavior.

Perception of a stressor and subsequent effects and consequences vary from one individual to another. On the other hand, it could be stated that some factors are more effective even on the person's perception of stress. Among these factors could be the person's genetic predisposition, temperament, ability to cope with stress, psychological resilience, cognitive processes, brain chemicals as well as gut microbiota. Early life stress also has a permanent effect on the HPA axis, causing a biologically-determined susceptibility to later stressors as well as psychological factors that cause predisposition to depressive affection. Similarly, studies demonstrated that early life problems (psychological stress) cause structural and functional changes in tracts such as the uncinate fasciculus, a white matter pathway that connects the amygdala to medial structures in the Prefrontal Cortex (PFC) (Dean and Keshavanb 2017, Ferrari and Villa 2017).

Psychological and physical stressors are perceived by the cerebral cortex, and they activate the HPA axis, which is a neuroendocrine pathway, causing the release of corticotropin-releasing hormone (CRH) from the hypothalamus. CRH stimulates the release of adrenocorticotrophic hormone (ACTH) in the anterior pituitary, which in turn initiates glucocorticoid synthesis in the adrenal cortex. Glucocorticoids such as corticosterone or cortisol, on the other hand, affect the HPA axis downstream, suppressing the production of CRH and ACTH. During this cycle, stress also induces the production and release of noradrenaline (norepinephrine) in the process of increased CR release. Noradrenaline and cortisol secretion cause bidirectional interaction on the HPA axis and leads to neurotoxic effects and cytokine release (Dean and Keshavanb 2017, Ferrari and Villa 2017). It is known that especially chronic stress causes many problems in the body such as irregular contractions in the gut muscles or triggers the disease. It was revealed that chronic stress, particularly stress-induced glucocorticoid release in the brain, caused disruptions in the prefrontal cortex and hippocampus, thereby affecting some aspects of cognitive processing (Popoli et al. 2012). It is also known that chronic stress changes the noradrenergic system, which is integrally related to the neuroendocrine and immune systems and that the hormone cortisol negatively affects immune system functions.

Researchers discovered that in some cases, bacteria communicate with the brain via the vagus nerve. The vagus nerve is the primary connection between the brain and the proximal gut tract. The humoral connection includes the HPA axis, which is responsible for regulating the stress response and gut endocrine cells as well as for secreting neuropeptides and gut peptide acting locally and on the brain via the vagus nerve and spinal cord afferent or blood brain barrier (Anglin et al. 2015). The vagus nerve can be viewed as a pathway for behavior change with anxiety (via gut inflammatory reaction) and anti-anxiety (via probiotics) effects (Bested et al. 2013). It was also found that the vagus is the main modulatory constitutive communication pathway between bacteria exposed to the gut and brain (Bravo et al. 2011). In this respect, the vagus nerve plays an important role in transmitting the changes in the GI system to the central nervous system (Forsythe et al. 2010).

There is also the possibility of physiological changes in the gut associated with Vagotomy (cutting of the vagus nerve), which may indirectly alter the functional properties of Lactobacillus (Bravo et al. 2011). When the vagus nerve is severed, the effects of gut bacteria on brain biochemistry, stress response and behavior are lost; however, communication can continue through other means, such as the immune system. Gut microbiota may play a role in stress response through communication established via vagus nerve and neurotransmitter release. Vagus nerve stimulation was defined as a successful approach to treat some of patients with treatment-resistant depression (Nemeroff et al. 2006), which further highlights the importance of the vagus nerve in modulation of behavior.

Some studies even established causal connections, and probiotic supplements were shown to reduce stress and cortisol levels in individuals (Eutamene and Bueno 2007). In addition, some studies demonstrated that chronic and social stress impaired the gut microbiota, thereby triggering the immune system response (Bailey et al. 2011, Gao et al. 2018).

In one study examining how stress-induced changes in gut microbiota affect health, beneficial bacteria were suppressed with a stressor, and as a result, it was seen that the overall diversity of the gut microbiota decreased and that overgrowth of harmful bacteria was reported, making animals more susceptible to infection and causing inflammation (Bailey et al. 2011).

On the other hand, it is also possible that the gut microbiota affects stress or other related mechanisms. In this respect, modulation of stress hormones (e.g. ACTH and corticosterone) by the gut microbiota is another approach that may explain the existing relationship (Heijtz et al. 2011). Animal models showed that male germ-free mice had an increased stress response with reduced hippocampal and cortical Brain-Derived Neurotrophic Factor (BDNF) and with reduced NR1 (NMDA receptor subunit) (hippocampus) and NR2A (hippocampus and cortex) (Sudo et al. 2004). Some probiotics have the potential to lower inflammatory cytokines, reduce oxidative stress and improve nutritional status (Logan and Katzman 2005, Brenner and Chey 2009). In a study with rats, it was shown that the stressor of maternal separation initiated the connection between the change in the gut microbiota and hypersensitivity to stress and that the triggering of this process could be prevented by supplementation of the probiotic Bifidobacterium bifidum G9-1 (Fukui et al. 2018).

Connections Between Gut Microbiota and Impulsivity

Impulsivity is among the basic locomotives of life. Humans need an impulse mechanism for vital actions such as feeding and reproduction. Impulse has cognitive, emotional and behavioral dimensions. Impulsivity, on the other hand, is associated with processes such as inability to resist urges, failure to delay gratification, seeking gratification, impatience, tendency to instant rewards, making decisions without thinking about impulses, and ignoring or not thinking about the possibility of getting harmed. The impulse causes the person to take action with intrinsic and extrinsic motivations. The frontal cortex area of the brain (especially the prefrontal and orbitofrontal areas) suppresses the mechanism of impulse that works alone. Impulse and the processes that impulse is associated with have a relationship with emotional and social maladjustment and it is an important factor in the basis of many psychiatric disorders of a person. Impulse usually manifests itself with its negative aspects and often occurs due to a disorder in the brain or as a result of human preferences and behaviors (Chamberlain and Sahakian 2007, Yazıcı and Yazıcı 2010, Stahl 2015).

Orbitofrontal cortex detects and evaluates the relationship between stimulus-reward. Sometimes, all these processes are evaluated cognitively before the action is taken, and accordingly, the action is behaviorally performed, delayed or postponed. Depending on the severity of the impulse or on the presence of an impulse disorder, the frontal cortex is less activated, whereas the regions responsible for the impulse are more activated (Holland and Gallagher 2004, Hornak et al. 2004).

Apart from the orbitofrontal cortex, among the regions that impulse and reward are responsible for is the nucleus accumbens, one of the basal ganglia, and the amygdala. In these areas, the relationship of neurotransmitters such as serotonin, dopamine and noradrenaline with impulse and reward is known. The decrease in the levels of these chemicals may therefore cause some control and function disorders, and at this point, the connection of the gut microbiota with neural transmission or the central nervous system was mentioned.

The effects of the interaction between the microbiota and the brain on social behavior have recently been demonstrated. In this respect, some contributions are expected in the contexts of cognition, emotion and behavior by using probiotic supplements. Some studies suggested that probiotic supplementation in adults was used for the effective treatment of impulsivity, which is the underlying mechanism of certain psychiatric disorders or problem behaviors (Arteaga-Henríquez et al. 2020). It is thought that probiotics have important contributions not only in impulsivity but also in the above-mentioned mechanisms. The basic mechanism of probiotics is to regulate the capacity of the gut microbiota, maintain the integrity of the gut barrier, prevent bacterial translocation, and regulate the local inflammatory reaction through the gut-related immune system (Rios et al. 2017). In addition, the contribution of probiotics in various indirect ways is observed. For example, it was seen that giving a probiotic supplement to a patient with anxiety disorder increased the amount of sleep and therefore reduced anxiety (Schnorr and Bachner 2016).

It is argued that a potential probiotic can strongly alter brain neurochemistry and behaviors related to anxiety and depression in mice (Bravo et al. 2011). Moreover, various probiotic supplements of Lactobacillus and Bifidobacterium are thought to have a neurochemical anxiolytic effect on the central nervous system and to be likely to reverse the regulation of the HPA axis (Bravo et al. 2011, Kane and Kinzel 2018).

Connections Between Gut Microbiota and Cognition Emotion Behavior

Cognitive Functions: Self-Control and Decision-Making

Bidirectional relationships between gut microbiota and cognitive processes or cognitive behaviors were demonstrated (Leblhuber et al. 2018). Gut microbiota composition may modulate cognition through different pathways that fit the brain-gut axis and may also cause cognitive dysfunction (Rogers et al. 2016, Blasco et al. 2017). Different studies revealed that the gut microbiota can directly affect brain functioning and modulate emotion, motivation and higher cognitive functions (executive and control processes) (Cryan and Dinan 2012, Borre et al. 2014, Dinan et al. 2014, Carabotti et al. 2015).

The concept of self-control is known to be associated with many problematic behaviors such as addictions and impulse disorders (Davis 2001, Oh 2003, Tangney et al. 2004, Kim et al. 2017). Furthermore, negative emotional states can cause a decrease in self-control (Sinha 2009) because negative emotions can trigger a loss of self-control by causing the person to focus more on his/her emotional state (Ward and Mann 2000).

Decision making, which is basically operated by the prefrontal cortex and which includes many complex cognitive functions, is the process of regulating one's emotions, thoughts and behaviors in accordance with his/her goals and environment (Paulus 2007). It is thought that the problem experienced in predicting the future can be attributed to impaired decision-making functions. Studies demonstrated the relationship of the problems seen in decision-making skills with addictions (Sun et al. 2009, Seok et al. 2015). Additionally, disorders such as anxiety and depression affect the individual's level of self-control as well as the decision-making pattern due to the problems in the prefrontal region of the brain.

The intolerance of uncertainty seen in the person with anxiety disorder causes him/her to avoid thinking about the future (Amir et al. 1998), which can quickly cause him/her to make inappropriate choices, even if they are unfavorable (Vythilingam et al. 2007). In addition, it is thought that the slow thinking process seen in individuals with depression is associated with the impaired decision-making ability. These individuals may not realize that the options available contain different values, and they may see the consequences of all options as similar. It is quite expected that this situation will affect the decision-making patterns (Paulus and Angela 2012).

Another argument for the existence of connections between gut microbiota and cognitive functions is that probiotics affect the decision-making mechanism, which is important among cognitive processes. It was reported that impaired cognitive structures and decision-making mechanisms, especially in patients with depression, could be improved in this way (Roman et al. 2018).

Emotions: Mood and Anxiety

It is thought that the gut microbiota have an effect on emotions, moods and eventually on behaviors (Bravo et al. 2011, Cryan and Dinan 2012, Roman et al. 2018). For instance, it is argued that depression and anxiety disorders, which play a role in the development of some problems such as addiction with cognitive, emotional and behavioral dimensions, are effective through neurotransmitter level (serotonin) and HPA axis (Skosnik and Cortes-Briones 2016).

The mechanisms underlying the formation of stress, fear and anxiety are shaped by genetic and environmental factors in the early stages of our life, and problems in brain development can lead to behavioral problems or psychiatric disorders such as depression, addiction and hypersensitivity to stress, which may be encountered in the future. Studies conducted in the last decade have shown that the gut microbiota can play an active role in these connections by affecting the development and functionality of the brain (Forsythe and Kunze 2013, Grenham et al. 2011). For example, a study focusing on emotional facial expressions associated with anxiety revealed the positive effect of microbiota on the activation of the prefrontal cortex, which has an important role in the regulation of emotions (Callaghan et al. 2017). In studies conducted with healthy adults, it was seen that long-term consumption of fermented milk products containing probiotics regulated the activation of certain brain regions, including emotion and emotional perception (Tillisch et al. 2013) and positively affected mood and anxiety levels (Messaoudi et al. 2011, Steenbergen et al. 2015). In another study, it was revealed that individuals with quite low mood levels had a significant improvement in their mood when they consumed food containing probiotics (Benton et al. 2007). Moreover, many studies involving animals showed the influence of gut microbiota on mood (Schroeder et al. 2007) and on stress response, anxiety-related behaviors and regulation of HPA activation (Neufeld et al. 2011, Clarke et al. 2013, Nishino et al. 2013).

Behaviors: Behavioral Addictions and Problematic Behaviors

It is known that the got microbiota increase dopamine release through bacteria such as *Escherichia* and *Bacillus* (Cryan and Dinan 2012, Skosnik and Cortes-Briones 2016). Problems in the dopamine system, which basically provides the motivation to demonstrate behaviors and which is defined as the basic structure of the sense of pleasure, can cause non-adaptive behaviors to be shown (Schultz et al. 1993, Koepp et al. 1998). Impairment observed in this system, especially polymorphism detected in the dopamine D2 receptor (Comings et al. 1996), was shown to be a serious risk factor for the development of behavioral addictions such as pathological gambling (Pallanti et al. 2010) or food addiction (Wang et al. 2001, Volkow et al. 2008). In a study conducted by Kim and colleagues (2011), it was revealed that the ratio of dopamine D2 receptors in the lower areas of the striatum decreased in individuals with Internet addiction. Studies focusing on Internet gaming addiction replicated the findings and showed increased dopamine release or differentiation at the dopamine D2 receptor level (Koepp et al. 1998, Han et al. 2007, Park et al. 2010). Based on these findings, it could be stated that the gut microbiota, known to regulate the amount of dopamine, are especially associated with problem behaviors or behavioral addictions. In addition, this relationship might be established on other cognitive and behavioral mechanisms such as impulsivity, self-control, decision making and difficulty in delaying gratification (Saville et al. 2010, Li et al. 2016), which has a relationship with addiction. Considering the serious effect of the eating pattern and the changes in this pattern on the gut microbiota as a mediator or regulatory factor in this relationship (Brown et al. 2012, David et al. 2014), it could be stated that sleep disorder, sedentary lifestyle and disordered and unhealthy diet brought about by addiction also play an important role in the brain-gut interaction.

Connections between Gut Microbiota and Psychiatric Disorders

Inflammatory response derived from unhealthy gut microbiota composition can disrupt the blood-brain barrier, causing neurodevelopmental problems, neuroinflammation and neurodegeneration. On the other hand, the brain-gut interaction seems to be related to psychiatric disorders such as depression and anxiety through various pathways and mechanisms. A fundamental mechanism for this lies in the connections between gut microbiota and cognition, emotion, and behavior, as mentioned above. In other words, the interaction between the brain and the gut can contribute to improvements or cause deterioration in the individual's cognition, emotion and behavior processes. From this point of view, it is easier for psychiatric disorders to emerge as a result of deterioration because there are studies showing that the bacteria have an important role in the bidirectional communication of the brain-intestinal axis and proving that certain bacteria could be useful therapeutic adjuncts in stress-related disorders such as anxiety and depression (Bravo et al. 2011).

Another basic mechanism could be through neurotransmitters and/or receptors such as dopamine and serotonin, which have functions in neural transmission. Depression and anxiety are highly complex psychiatric disorders with various etiologies, including genetic, epigenetic, and environmental factors. The disorder itself has a variety of pathophysiological mechanisms according to altered neural circuits and the pathology such as inflammation or an increased stress response. Clinical studies proved that the noradrenaline and serotonin neurotransmitter systems play a role in depression and anxiety. The connections between the gut microbiota and some neurotransmitters and their receptors were discussed above. Research revealed several mechanisms, including altered serotonergic, noradrenergic, dopaminergic, and glutamatergic systems, increased inflammation, HPA axis abnormalities, decreased neurogenesis and neuroplasticity (Dean and Keshavanb 2017, Ferrari and Villa 2017). The amygdala and hippocampus are the brain regions associated most with depression. Depression is characterized particularly by dysfunction of the monoamine neurotransmitters in particular. In depression, certain effects are observed in relation to neuroendocrine axes in the brain. Altered activities of HPA axis are important biological findings in depression and anxiety disorders (Dean and Keshavanb 2017, Ferrari and Villa 2017).

Undoubtedly, many factors such as HPA, endocrine system, sleep, exercise and eating patterns have a holistic effect on the neural transmission mechanism or the central nervous system. In particular, the eating pattern is thought to be effective in the formation of many chronic diseases, including depression, Parkinson's Disease and various neuropsychiatric disorders (Mizunoya et al. 2013, Myles 2014). In addition, disorders in HPA play an important role in the formation of other problems including depression and anxiety behaviors and disorders (Naseribafrouei et al. 2014). At this point, the use of probiotic bacteria treatments targeting HPA activation in acute physiological stress treatment supports the relationship between microbiota, HPA, psychiatric disorders and stress. Moreover, proteins that can be regulated by the gut microbiota, such as synaptophysin, were found to have a regulatory effect on long-term synaptic transmission that influences anxiety-related behaviors (Heijtz et al. 2011).

As seen above, various neurotransmitter systems have quite a big role in many psychiatric or behavioral disorders such as depression and anxiety. It was shown that beneficial bacteria can calm anxiety-prone mice, while disease-causing or harmful bacteria can increase depression and anxiety. Gut bacteria also produce hundreds of neurochemicals that the brain uses to regulate basic physiological processes and mental processes such as learning and memory. For example, gut bacteria produce up to 95% of the serotonin supply, which affects both psychological state of the body and GI activity and produce 50% of dopamine, which is a neurotransmitter associated with learning, motivation, and pleasure (Moelling 2016, Dinan and Cryan 2017).

Some studies showed that abnormalities in the gut microbiota were associated with cognitive problems, anxiety, depression, autism, and schizophrenia and were influential on neuronal plasticity and neurotransmitter (serotonin, dopamine) levels (Burokas 2015). Improving these abnormalities in the microbiota are likely to be effective in alleviating psychiatric disorders such as depression (Liang et al. 2018). In some other studies, it was reported that the use of probiotics brings improvement in depression and anxiety measures (Messaoudi et al. 2011). The combination of *Lactobacillus helveticus* and *Bifidobacterium longum* was shown to reduce anxiety in rats and to have beneficial psychological effects in humans resulting from a decrease in serum cortisol (Messaoudi et al. 2010). Exposure to microbial pathogens was also observed to lead to behavioral abnormalities, including anxiety-like behavior and impaired cognitive function (Sullivan et al. 2006, Goehler et al. 2008). It was revealed that antidepressant-like behaviors could be modulated with the use of *Bifidobacterium infantis* in the forced swim test, which is a model frequently used for the evaluation of pharmacological antidepressant activity (Cryan et al. 2005, Desbonnet et al. 2008).

Modulation of proteins like PSD-95 by the gut microbiota may lead to long-term modulation of synaptic transmission affecting motor control and anxiety-like behavior in adult life (Heijtz et al. 2011). On the other hand, transferring fecal matter from depressed individuals to germ-free rats was reported to cause depressive behavior in rats (Kelly et al. 2016). In one study, mice were infected with a parasite to induce chronic, low-grade gut inflammation. In addition to causing gut inflammation, this implementation was shown to suppress BDNF levels in the hippocampus and to cause the mice to behave more anxiously. When the mice were then treated with the beneficial microbe Bifidobacterium longum for 10 days, their behavior and BDNF levels returned to normal (Bercik et al. 2010).

Altered fecal microbial composition, characterized by higher numbers of *Enterobacteriaceae* and *Alistipes* but fewer *Faecalibacterium*, was observed in individuals with depression. It was also reported that *Bacteroidales* was over-represented in individuals with depression and that members of the *Lachnospiraceae* family were under-represented. It was seen that daily consumption of certain probiotic species (*B. bifidum W23, B. lactis W52, L. acidophilus W37, L. brevis W63, L. casei W56, L. salivarius W24 and L. lactis*) significantly reduced vulnerability to depression, anxiety or negative mood. Meta-analysis studies also revealed that probiotics significantly reduced depression scores. In some studies, probiotic supplements showed a significant effect in individuals with mild-to-moderate depression (Naseribafrouei et al. 2014, Steenbergen et al. 2015, Jiang et al. 2015, Huang et al. 2016, Pirbaglou et al. 2016).

Depression and anxiety can also be defined as a neuropsychiatric disorder with neurodevelopmental problems at its origin, especially considering the developmental dimensions of genetic and environmental factors (Ansorge et al. 2007, Leonardo and Hen 2008). Various studies investigating depression from a neurodevelopmental perspective have begun to be encountered frequently. Some researchers studying on the etiology of depression introduced the "Neurodevelopmental Theory" to emphasize the importance and influence of the early stages of human life, including the prenatal period, on the occurrence of depressive disorders (Gałecki and Talarowska 2018). In a similar context, some microbial-derived metabolites were associated with metabolic, neurodegenerative, and neurodevelopmental disorders (Dambrova et al. 2016, Li et al. 2018, Vogt et al. 2018). Studies showed that neurodevelopmental disorders such as autism, schizophrenia, attention deficit and hyperactivity disorder have a relationship with microbial pathogen infections in the perinatal period (Mittal et al. 2008, Petra et al. 2015).

Discussion

The changes in human physiology and psychology in the state of balance or imbalance of the gut microbiota, or in its various compositions, are quite exciting. Therefore, researchers continue their studies on this subject without slowing down. As the studies continue, the number of new supporting findings is increasing day by day.

There appears to be a clear bidirectional communication between the brain and gut microbiota (Grenham et al. 2011, Zalar et al. 2018, Stasi et al. 2019). However, actors and information regarding all the systems involved in this communication are not yet available because the brain-gut connection brings up the interaction of physiological and psychological processes, and this interaction reveals the role of many factors that make it difficult to use the reductionist approach. Although different or opposite findings were obtained in some studies, it could be stated that as a general mechanism, the gut microbiota modulates brain function and development and that the brain can alter the gut microbiota by allowing colonization by pathogenic bacteria (Bravo et al. 2011, Cryan and Dinan 2012, Galley and Bailey 2014, Ming et al. 2018).

Bidirectional communication between the brain and gut basically occurs in three different ways: I) Neural (mainly by the vagus nerve and enteric nervous system), II) endocrine (cortisol) and immune (cytokines), and finally III) stress (HPA axis) (Bercik and Collins 2014, De Palma et al. 2014, Carabotti et al. 2015, Petra et al. 2015, Sherwin et al. 2016). Undoubtedly, this classification or communication ways can be put forward in different forms or formulations. However, the classification made in this study was based on the findings and prominent concepts.

It is seen that most of the research on understanding the connections between the brain and the gut has been conducted on rodents (Sudo et al. 2004, Neufeld et al. 2010, Fukui et al. 2018). However, in recent years, with the development of technology, similar mechanisms have been started to be investigated in humans. Better understanding of this connection in humans is more difficult due to the involvement of more complex systems, and more research is thus needed. Even a healthy microbiota composition has not yet been defined with precise descriptions. In some studies, positive effects of even a single type of beneficial bacteria were observed on mental health and behavior, though. It was seen that some probiotic strains can modulate various aspects of the microbiota-gut-brain axis, depending on the type of bacteria. Furthermore, the data obtained revealed the existence of a clear ability of probiotics and potential probiotic strains to modulate brain and behavior and to improve mental health (Järbrink-Sehgal and Andreasson 2020). On the other hand, as it was emphasized in Figure 1, it would not be correct to explain the brain-gut connection through a single factor such as probiotics or eating patterns. It should be considered that factors such as cognition, emotion and behavior as well as sleep, exercise and eating behavior interact with each other and that brain-gut connection is formed in a holistic process. For example, although some studies showed that probiotic supplements had positive effects against stress, depression, anxiety and inflammation in individuals, failure to observe these contributions in every individual was explained with different accompanying factors that vary from one individual to another (Romijn et al. 2017).

In this study, the interactions of the brain-gut axis with cognitive, emotional, behavioral and physiological processes were examined, while the reivew of the literature was limited to certain emotions and behaviors, neurodevelopmental problems and cognitive mechanisms. For example, cognitive processes were handled through self-control and decision making, and psychiatric disorders were discussed over depression and anxiety. Eventually, the related relationships were examined through these sample variables. Undoubtedly, this was not merely because of imposing a limitation due to the wide scope, but also because there were many intersections and interactions between these mechanisms. For example, research indicates the existence of connections between the gut microbiota and some basic cognitive and behavioral dynamics of the brain, such as decision making, impulse and self-control (Benton et al. 2007, Cryan and Dinan 2012, Borre et al. 2014, Dinan et al. 2014, Blasco et al. 2017, Leblhuber et al. 2018). From this point of view, the same connections can be seen in other patterns on which these dynamics are based, such as especially problem behaviors and behavioral addictions. In other words, a person with a healthy microbiota composition may have a lower risk of developing problem behaviors and behavioral addictions. There are many psychosocial factors that play a role in the development of behavioral addictions (Young and Rodgers 1998, Aydın and Volkan 2011, Lee et al. 2014, Lee et al. 2018, Savolainen et al. 2020). Accordingly, it is known that brain functions and neurotransmitter systems have a role in most of the processes of impulsivity, decreased emotional well-being, low self-perception, loneliness, inadequate social behaviors, social anxiety, increased psychological stress, emotional inbalance and weakness in self-regulation (Coccaro and Kavoussi 1996, Chamberlain and Sahakian 2007, Neufeld et al. 2011, Zhang et al. 2014, Dean and Keshavanb 2017, Ferrari and Villa 2017, Mumtaz et al. 2018, Lam et al. 2021). Most of the time, the opposite of this process seems possible. After a while, addicted individuals may experience sleep disorders, insufficient exercise, inadequate or unhealthy nutrition and mood disorders (Bener and Bhugra 2013, Park 2014, Khan et al. 2017, Zhang and Wu 2020). For this reason, the gut microbiota might be deteriorated.

Conclusion

Consequently, processes related to cognitive, emotional, behavioral and physiological factors (including problematic behavior or disorders in the brain based on these processes) appear to be connected with the gut microbiota through the neural, endocrine/immune and HPA axis. In addition, the bidirectional connections between the gut microbiota and psychiatric disorders, problem behaviors and behavioral addictions are affected by the interaction of various patterns in which cognitive/emotional processes and hormones/neurotransmitters play a role.

Another result of this research is the existence of strong connections between physiological, psychiatric and psychological mechanisms. As shown in this study, the relevant connections revealed that not only cognitive, emotional and behavioral issues related to human beings but also issues such as nutrition, sleep and exercise should be considered together and that there are intertwined relationships affecting each other.

Findings reported in the related literature are important in terms of the development of new treatment methods aiming to regulate the brain-gut connection as well as with respect to the use of probiotics in the treatment of various disorders such as depression and anxiety, problematic behaviors and cognitive disorders (Dinan and Cryan 2013). In this respect, there is a need for studies in which these connections will be revealed empirically and which will examine each variable individually as well as all the variables holistically.

Authors Contributions: *The authors attest that they have made an important scientific contribution to the study and has assisted with the drafting or revising of the manuscript.*
Peer-review: *Externally peer-reviewed.*
Conflict of Interest: *No conflict of interest was declared by the authors.*
Financial Disclosure: *The authors declared that this study has received no financial support.*

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