

Chapter

The Role of Gut Microbiota in Cognitive Impairment

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Abstract

This chapter focuses on the activation and modulating function of the gut-brain axis in relation to memory and other cognitive functions. The gut-brain axis is a two-way communication system between the gastrointestinal system and the brain, closely regulated by the gut microbiota. Recent studies show that gut microbiota can modulate memory through neuroinflammation, neurotransmitter interactions, and effects on synaptic plasticity. Disruption of the gut microbiota, known as gut dysbiosis, has been linked to cognitive disorders and neurodegenerative diseases. This chapter will look at the effects of the gut microbiota on memory and explain how the pathways and signaling through the microbiota affect this relationship. It will also examine therapies that are thought to regulate the composition of the human gut microbiota to improve one's memory and prevent aging. Additionally, the chapter discusses how gut-targeted therapies may be promising approaches toward enhancing cognitive health and optimal memory performance.

Keywords: gut-brain axis, gut dysbiosis, gut microbiota, memory, neurodegenerative diseases

1. Introduction

The human gut is also called the second brain and houses a complex, relatively independent network of neurons localized in the intestinal wall called the enteric nervous system (ENS) [1]. This network of neurons has a crucial role in the modulation of numerous GI functions such as motor, secretory, and circulatory blood flow [2]. Several crucial features of the ENS include its capacity for the biosynthesis and release of many types of neurotransmitters known to be used in the CNS, including serotonin, dopamine, and gamma-aminobutyric acid (GABA) [3].

Every neurotransmitter system has a distinct and crucial role to perform in retaining the normal physiological function of the nervous system. As chemical messengers between neurons, neurotransmitters act to organize various activities, including controlling mood, muscle movement, thought processes, metabolism, and more. Proper functioning of these systems is necessary for a body to be healthy, since any

derailment results in several neurological and psychological issues. The cholinergic subgroup includes neurons that utilize the primary messenger acetylcholine in the transmission of nerve impulses. This neurotransmitter plays a vital role in several neurological and psychophysiological aspects, including sensory-motor functions, sleep–wake and attention-arousal systems, and cognitive behaviors related to learning and memory [4]. The glutamatergic system is made up of those neurons that contain glutamate as one of the major released neurotransmitters. This system is important in many activities of the human brain, and more so in learning and memory activities [5]. Meanwhile, the network of the GABAergic system contains neurons that release gamma-aminobutyric acid (GABA); GABA is an inhibitory transmitter that stops or prevents the continuation of some impulses to limit specific actions. It has an important function in controlling anxiety, alertness, muscle tone, learning, and epileptic activity [6].

The chemical or molecular communicators of the aminergic, monoaminergic, or biogenic amine system include dopamine, serotonin, histamine, and norepinephrine. The dopaminergic system comprises neurons that synthesize dopamine, which is an endogenous catecholamine necessary for control of behavior and physiological processes such as movement and cognition. Notably, 90% of serotonin is synthesized in the gut, which influences bowel movement and has an impact on mood and social conduct. Similarly, the dopamine secreted in the GI tract is related to the movement of the gut and, reportedly, to moods and emotions [7, 8]. A further factor that is crucial in the balance of the gut-brain axis (GBA) is the gut microbiota—a vast population of microbes that reside in the gut. These microbes are not just residents within the gut but are functioning as members of the intestinal microbiome that play an integral part in coordinating gut-brain interaction. Our microbial partners exert an effect on the brain by generating intermediate products like SCFAs and regulating neurotransmitter concentrations [9].

The gut-brain axis refers to the mechanistic pathway by which the ENS and CNS are connected and transmit signals and information between the gut and the brain, respectively. This axis is associated with neural networks such as the vagus nerve, together with endocrine and immunologic systems. Certain chemicals produced in the digestive tract can impact the mind in some ways; for example, gut serotonin affects mood and is associated with diseases like anxiety and depression. Similarly, changes in gut bacteria affect the synthesis of neuromodulators such as GABA and could influence stress and cognition [10]. Furthermore, many of these neurotransmitter interactions have ties to essential metabolic processes, underscoring how neural signaling and metabolism are interlinked within the gut.

In addition to its role in neurotransmitter regulation, the gut microbiota also plays a crucial role in metabolic processes. Literature reviews suggest that overall changes in the gut microbial community, including a decrease in microbial richness, are linked with metabolic dysregulation and obesity. Nevertheless, research findings on the relative composition of microbiota in obese subjects are somewhat contradictory. This contradiction simply cannot be overstated as it varies with other factors such as gut microbiota, diets, genes, and the surrounding environment [11]. A primary way through which the microbiota creates metabolic effects is by the production of short-chain fatty acids (SCFAs). These microbial metabolites help in maintaining energy currency through changes in some gut hormones, such as cholecystokinin (CCK), glucagon-like peptide 1 (GLP-1), peptide tyrosine-tyrosine (PYY), and leptin. These hormones govern hunger, energy management, and glucose metabolism; therefore, it is possible to assume that the gut microbiota is a main mediator of metabolism [12].

Memory and cognitive activities are central elements in human existence, since they can be supported by learning, critical thinking, and decision making. The next mental organ is the second brain located in the intestines; it has an obligatory connection with the first one—the brain; the microbiota in the gastrointestinal tract affects the brain through several links. The gut microbiota plays a crucial role in producing serotonin, dopamine, and gamma-aminobutyric acid (GABA), which are essential signaling molecules for brain function. Several studies have demonstrated that changes in gut microbiota can modulate neurotransmitter synthesis and then influence cognition and mood. That is, *Lactobacillus* and *Bifidobacterium* improve serotonin production that is crucial for regulating moods and forming memories [13, 14].

A healthy gut microbiota and a stable composition prevent excessive immune activation in the body. Chronic inflammation has been attributed to cognitive deterioration, and dysbiosis-related inflammation has been linked to neurodegenerative diseases, including Alzheimer's. This high-level overview is designed to reflect the evidence about how the gut microbiota helps in the regulation of immunities that are important in preserving and maintaining the health of the neural functions and cognitive abilities [15].

The disruption of gut microbiota, commonly called dysbiosis, or microbial dysfunction, has been associated with smaller hippocampal size and memory deficits. As previous animal experiments have also pointed out, when the gut microbiota composition has been shifted through FM, cognitive ability is affected. Human studies also back these findings by linking gut health to different cognitive disorders, including Alzheimer's and Parkinson's disease [16].

Gut microbiota is the community of microbes inhabiting the rumen and other parts of the gastrointestinal tracts that, through the gut-brain signaling, significantly affects cognition. This two-way communication net showcases neural, immune, and endocrine systems, and a new investigation underscores the importance of this axis for memory and learning as well as general cerebral function [17]. Research shows that a person's gut microbial composition correlates with the brain's efficiency, as is seen from the following studies. In middle-aged adults from the CARDIA study, the microbial community targeting β -diversity shows linear associations with better cognitive test scores across different domains, such as the Montreal Cognitive Assessment and category fluency tests. Of those, *Barnesiella* and *Lachnospiraceae* were positively correlated with better cognitive scores, and *Sutterella* with worse scores [18]. Based on these findings, it would be possible to state that microbial diversity plays a crucial role in protecting cognition.

Altered gut microbiota or dysbiosis has already been linked to certain cognitive decline and neurodegenerative diseases, including Alzheimer's. Chronic stress has also been known to cause alterations in gut microbiota, causing inflammation and thereby disrupting the communication channels of the body. A work using germ-free mice showed that mice that received microbiota from a stressed mouse showed reduced memory and increased anxiety-like behavior [19, 20]. Overall, these findings provide preliminary evidence that improved microbiota may help safeguard good cognitive health and counteract the deleterious effects of chronic stress.

Specifically, the gut microbiota that humans develop from infancy directly affects their brain. Sanitized animals have decreased learning abilities and poorer basal memory, pointing to the fact that microbiota is essential for proper brain functions. Consequently, the effects of probiotics, including specific strains of *Lactobacillus*, on memory in animal models have been demonstrated, and the research proves that the gut microbiota plays a role in early cognitive health [19, 20].

2. About the gut microbiota

The effect of the gut microbiota on human health has been recognized as an important field of study. The gut microbiota is a community of microorganisms that live in the digestive tracts of humans and animals, even insects. The human body contains the greatest number of microorganisms and the most diverse range of species in the body [21]. They are made up of thousands of microorganisms, such as bacteria, viruses, and some eukaryotes, which settle in the digestive tract soon after birth [22].

The term “human gut microbiota” can be defined as a body of microbial organisms—bacteria, fungi, and viruses—their genetic material, and waste products established in the digestive system. The gut microbiota is one of the largest and most diverse microbial communities of the human body, which is estimated to contain trillions of microbes. These microorganisms have an active role in various functions within the body, which include digestion, immune system regulation, and biosynthesis of various elements within the body [23].

The gut microbiota is also responsible for breaking down some of the intricate carbohydrates, which could not be broken down in the body independently. It assists in producing important body vitamins such as vitamin K and the B group of vitamins, besides controlling immune responses. In this way, the microbiota competes with pathogenic microbes for space and nutrients and thus helps to prevent the invasion by pathogens as part of the immune defense system [24].

Another dynamically evolving area is the fact that the gut microbiota synthesizes bioactive metabolites, in particular, SCFAs that contribute to the anti-inflammatory potential and the mucus layer of the gut. These SCFAs, and other metabolites, not only affect the local intestinal health but also physiological functions throughout the body. Further, the gut microbiota interacts with the brain through the gut-brain axis, releasing neurotransmitters, including serotonin, which influence moods, cognitive abilities, and overall mental well-being [25].

The structure of the gut microbiota is determined by the presence and density of each microbial species, which can significantly differ between people. Two major bacterial phyla that form a large part of the human gut microbiome are Firmicutes and Bacteroidetes, which have been widely investigated. It is hypothesized that the Firmicutes/Bacteroidetes (F/B) ratio might be used as a biomarker associated with specific diseases: an increased F/B ratio is proportional to obesity and metabolic disease. More specifically, Firmicutes are better designed to mine energy from a meal, while those with a high Bacteroidetes profile are generally lean [26].

Nevertheless, the F/B ratio alone does not give a complete representation of the state of the guts or the gut microbiota. Other groups of microbes that play a role in the gut include: Proteobacteria, Actinobacteria, and Verrucomicrobia. Fluctuations in the levels of these microbes have been linked to inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), as well as other bowel disorders. The Microbiological profile of the microbiome may also change depending on the diseases: some microbial taxa are associated with IBD, obesity, cardiovascular disease, and even psychiatric diseases such as depression and anxiety [27].

The body needs to maintain a diverse gut microbiota because the imbalance of microbial systems contributes significantly to health problems. Quantitative data derived from microbial profiling have shown that dysbiosis is related to gastrointestinal disorders like IBS, GERD, and IBD. As for the aspect of metabolic health, dysbiosis has been linked with some disorders, such as obesity, type 2 diabetes, and cardiovascular diseases, thought to be influenced by the change in microbial fermentation profile and

its subsequent impact on nutrient metabolism [28]. Also, the gut microbiome concerns directly psychological state and cognition through the production of brain hormones such as serotonin [29]. When the balance in the microbiome is disturbed, this results in psychophysical disorders that affect a person's emotional state; these include depression, anxiety, and the autistic spectrum disorder (ASD). Therefore, keeping the microbiome in a state that ensures health is imperative to digestive, metabolic, and mental health [30].

3. The gut-brain axis: A two-way communication system

“It has been thought for quite a long time that the gut and the brain are two discrete entities that do not necessarily communicate with each other but it is now known that in fact they are two integrated partners, and the ongoing ‘discussion’ between the two influences not only digestion but also mood, memory, and over all wellbeing” [31, 32].

The gut-brain axis (GBA) is a two-way communication system that involves the central nervous system (CNS) and the gastrointestinal tract (GIT) through neural, hormonal, and immunological signals to modulate how the body responds to stress, inflammation, and infection, while regulating the physiological functions associated with the CNS [31, 33].

This bidirectional system is between the CNS and the GIT, as shown by studies on the elements that facilitate communication between the CNS and the enteric nervous system (ENS). It comprises complex interactions through components such as the vagal nerve, the hypothalamic–pituitary–adrenal (HPA) axis, immune signaling, and the gut microbiota [34, 35].

Key components of the gut-brain axis

- *Vagus nerve*: A neuronal pathway that directly links the gastrointestinal tract and the brain.
- *Hypothalamic–pituitary–adrenal (HPA) axis*: Regulates stress responses by the transmission of endocrine signals.
- *Immune system*: Microbes and systems use cytokines and chemokines as signal molecules.
- *Gut microbiota*: Produces metabolites such as short-chain fatty acids (SCFAs) as well as neurotransmitters that have an impact on brain function [35, 36].

It could be seen that several bidirectional communication mechanisms exist between the gut microbiome, the gut, and the brain. In principle, signals from gut microbiota and specialized cells of the gut endocrine, neurocrine, and inflammation-related all reach the brain. As a result, the brain can modulate microbial communities and their activity by endocrine and neural pathways. Seven pathways of care are shown in **Figure 1** [37].

Key pathways

- *Efferent signals*: Brain→Gut—via neuroendocrine output, autonomic output, and HPA output.
- *Afferent signals*: Gut→Brain—by hormones, cytokines, and sensation from the gut.

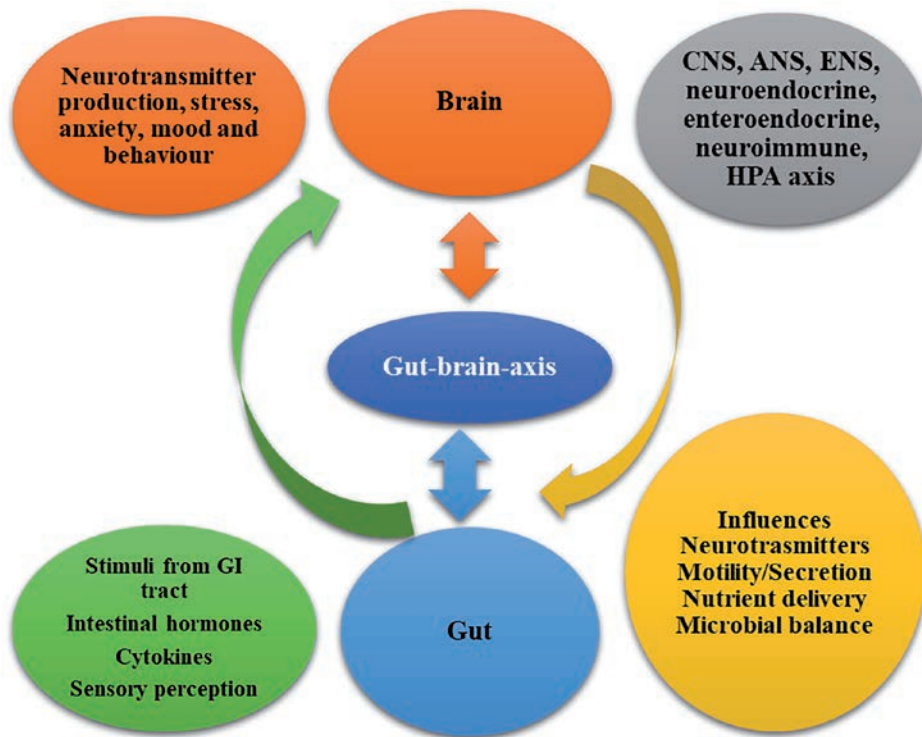


Figure 1.

The gut-brain axis represents bidirectional communication between the gut and brain, involving 'top-down' (brain-to-gut) and 'bottom-up' (gut-to-brain) pathways. These signals are mediated by systems such as the CNS, ANS, ENS, neuroendocrine, enteroendocrine, neuroimmune, and the HPA axis. In a healthy state, these pathways maintain gut and brain function. Brain-derived signals regulate gut motility, secretion, nutrient supply, and microbial balance. Conversely, gut-derived signals—such as hormones, cytokines, and sensory input—influence neurotransmitter production, stress, mood, and behavior [37].

3.1 Mechanisms of communication: Neural, hormonal, and immune pathways

The gut-to-brain axis contains two major pathways: afferents, which relay gut information, including nodose vagal and dorsal root ganglia (DRG) that convey information to the CNS through the vagus and spinal sensory nerves, respectively; herein gut-derived hormones and neurotransmitters, circulating inflammatory and immune-related signals [38].

3.1.1 Neural pathways

The neural pathways act as a basis of connecting the gut with the brain through a network of neural connections.

Enteric nervous system (ENS), also known as the second brain, is part of a connective neural tissue located in the intestinal wall. Horbacz, Pawlak, and Konturek concluded that reflex arcs within ENS regulate gut motility, secretion, and blood flow individually. These reflexes are local, but they also involve vagal and spinal afferent fibers for conveying sensory data to the CNS for synchronized digestive functions [39, 40].

The parasympathetic nervous system, for which the vagus nerve is a key part of is relied upon as the major information path between the gut and the brain. It also relays information from the gut to the brainstem, or the gut's nutrient presence or its distension. In response, the brainstem then regulates motor details falling under the gastrointestinal system, changing motility and secretion necessary [33, 41].

While vagal signaling dampens inflammation overall in the body, spinal nerves relay pain and inflammatory messages from the intestinal tract to the CNS. This pathway is especially significant in conditions where the patient is sensitive to gut stimuli, like IBS [31].

These signals that are received from the gut get to the brain stem, hypothalamus, and limbic system, therefore affecting responses to stress, moods, and even decisions made. For example, signals arising from the gut can initiate the HPA axis during stress, and there are systematic response changes [42].

In the gut-brain axis, hormonal circuits are one of the methods through which signals move from the gastrointestinal system to the CNS. Subsequent research has further refined the understanding of several hormonal integrations involving the gut-brain axis and emphasized the critical functions of the gut-born neurotransmitters and hormones in the regulation of physiological balance. Serotonin, mainly synthesized in GIT, has been studied for a long time, probably because of its multiple effects on gastrointestinal motility as well as central nervous activities. Recent studies have provided evidence that changes to the gut microbiota could have a marked effect on serotonin production and thus influence a person's moods and cognitive abilities [43, 44]. This serotonin production is controlled by the microbiota, which in turn can alter the synthesis and release of these molecules. After its synthesis, serotonin works in the brain by using the vagus nerve or by blood-borne method, regulating emotions and conduct [31].

Besides, the impact of the gut microbiota in synthesizing the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) has been attracting focus. Some bacteria have been found to biosynthesize GABA, some of which affect the local gut ecosystem as well as the CNS relief [43].

In addition, interactions between ghrelin, leptin, and the CNS have been further described. Though ghrelin was initially discovered to regulate food intake, it seems to have several functions other than energy balance, including the regulation of mood and cognitive functions, which is also true for leptin, apart from its role in signaling satiety [45].

4. Gut microbiota and cognitive function

4.1 Neuroinflammation and cognitive decline

Neuroinflammation, which activates the brain's immune cells, plays a crucial role in cognitive impairment. Microglia are the resident immune cells in the brain with a critical role in promoting healthy neural responses. However, constant stimulation of these cells results in the persistent production of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF- α), interleukin-6 (IL-6), and interleukin-1 β (IL-1 β). Even though these molecules are helpful in cases of acute inflammation, chronic synthesis of these molecules affects the synaptic plasticity and impairs neuron signaling and promotes neurodegeneration. This leads to inflammation, which injures neural circuits that are involved in learning and memory, and therefore contributes to the development of progressive cognitive decline [46].

One of the long-term trends that stems from the outlined neuroinflammation is the disruption of the so-called blood–brain barrier (BBB), which prevents some substances from getting into the brain. Inflammation disrupts the integrity of the BBB in chronic inflammation and allows peripheral inflammatory mediators, immune cells, and toxins to penetrate the CNS [47]. This breach also worsens inflammatory processes and increases the rate of neuronal damage. Neuroinflammation also activates the release of ROS, which leads to oxidative stress at the same time. These ROS affect neurons and synapses, leading to the aggravation of structural and functional abnormalities of the brain connectivity and selectively in the hippocampal region implicated in memory [48].

Neuroinflammation is well associated with neurodegenerative diseases, including Alzheimer's disease. These pro-inflammatory cytokines promote the formation of amyloid-beta plaques and the pathologic accumulation of hyperphosphorylated tau in Alzheimer's disease. These abnormal protein deposits exacerbate inflammation and speed up neuronal loss, which forms a dangerous feedback loop that heightens cognitive loss. Such an involvement of inflammation and neurodegenerative pathology implies that neuroinflammation should be targeted in therapeutic approaches [49].

Chronic inflammation is a prime cause since the general regulation of immunity weakens as a person grows older. Also, gut dysbiosis is an abnormal microbial ecosystem in the gut, and this affects the inflammation that flows along the gut-brain axis. Other aspects of the primary neuroinflammation include modifiable lifestyle factors, including unhealthy diet, lack of physical activity, chronic stress, and sleep deprivation, all of which contribute to additional aspects of neuroinflammation.

4.2 Neurotransmitter production and synaptic plasticity

The biogenesis of neurotransmitters and related functions in synaptic plasticity are inherent to the process of neural transmission, learning, and memory. The dorsal striatum, which forms a key part of the forebrain and constitutes a major part of what is perhaps the most intricate component of the brain involved in action control and learning, can illustrate this paradox vividly. In this area, dopaminergic, glutamatergic, and endocannabinoidic systems modulate both the afferent and efferent activities of medium spiny neurons (MSNs), the major type of neurons in the striatum. These interactions support two major forms of long-lasting synaptic plasticity, that is, long term potentiation (LTP) and long term depression (LTD) [50].

LTP at these inputs is governed by N-Methyl D-Aspartate (NMDA) receptors and may involve dopamine D1 or adenosine A2A receptors on the medium spiny neurons (MSNs). Calcium influx triggered by LTP activates calmodulin-dependent pathways (e.g., CaMKII) and calmodulin-independent mechanisms, driving synaptic modifications such as AMPA receptor insertion. These adaptations potentiate synaptic efficacy, underlying goal-directed learning and skill acquisition [51, 52].

In contrast, LTD involves retrograde endocannabinoid signaling, initiated by activation of metabotropic glutamate receptors (mGluRs) and dopamine D2 receptors [53]. This process reduces neurotransmitter release probability at presynaptic terminals, influencing the plasticity required for habit learning. This bidirectional modulation of synaptic strength (LTP and LTD) enables the striatum to support diverse learning paradigms, such as the transition from goal-directed actions to habitual behaviors as tasks are repeated and automatized [50, 54].

The striatal neuromodulation is further influenced by the interaction effect between different neurotransmitters. For example, dopamine regulates glutamate and GABA inputs in the output neurons in the striatum to regulate the excitation and inhibition required in the timing and selection of motor and other actions [55]. These endocannabinoids, acting through specific CB1 receptors, are known to play a profound role in the regulation of LTD at both the excitatory and inhibitory synapses. These mechanisms underline the basic tenets of two processes carried out by neurotransmitters, namely the direct interactions at the synaptic level and long-term adaptive forms [56].

The complex activity of neurotransmitters in the regulation of synapses and synaptic plasticity has even put them at the vanguard of cognition and behavior. Dopaminergic signaling is especially important consistently in the initial learning involving LTP and habitual learning involving LTD. The overlapping and integration of these neurotransmitter systems within the striatum allows the fine tuning of the neural circuits and thus learning and desirable behavior. These considerations also provide avenues for casting a therapeutic net for neuropsychiatric diseases characterized by abrogated plasticity, such as Parkinson's disease, which tilts the balance and undermines the graceful functions of these highly regulated circuits by virtue of aberrant dopaminergic neurotransmission [57].

5. Pathways and signaling of the gut-brain axis and memory: Bridging the gap

5.1 Immune pathways and neuroinflammation

The term neuroinflammation refers to the activation of the body's immune system response mechanisms, focusing specifically on the immune activity taking place within the CNS, and for good and bad, neuroinflammation is a process that is central to maintaining brain health. Just as acute neuroinflammation is protective through clearance of infection and repair of neural damage, chronic or uncontrolled neuroinflammation is implicated in neurodegeneration and cognitive decline. Neuroimmunology refers to the processes by which immune responses contribute to neuroinflammation, and this comprises complex interactions between resident immune cells, extravasated cytokines, and circulating inflammatory mediators.

Microglia, which are the macrophages of the central nervous system, form the fulcrum of neuroinflammation. These cells become active in response to the injury of tissue, infection, or the presence of neurotoxic substances. Once activated, the microglia assume the reactive state and begin to release presynaptic cytokines, including tumor necrosis factor- α (TNF- α), interleukin 6 (IL-6), and interleukin 1-beta (IL-1 β). These cytokines can interfere with the normal process of synaptic transmission, hinder communication between neurons, and compromise the integrity of the BBB, allowing for the influx of additional leukocytes from the periphery and escalating neuroinflammation [58].

Toll-like receptor signaling is one of the major pathways through which an immune response is elicited in the CNS. Among those, TLR4 is engaged by LPS derived from bacterial infections, and subsequent activation of the NF- κ B pathway. NF- κ B migrates to the nucleus to promote the degradation of genes that manufacture further pro-inflammatory cytokines and enzymes like inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2), and sustain inflammation [59].

Oxidative stress is another feature that is evident in neuroinflammation and will be discussed next. Activated microglia release reactive oxygen species and nitric oxide, both of which have toxic effects on neurons, compromise the integrity of mitochondria, and antagonize synaptic plasticity. These reactive molecules build up in the brain and cause damage linked to neurodegenerative disorders such as Alzheimer's disease and Parkinson's disease [60].

Prostaglandins produced following the COX-2 pathway are further well-known inflammatory mediators in neuroinflammation. Related to PGE₂ are neuronal excitotoxicity, synaptic dysfunction, and cognitive impairment. Blocking the COX-2 pathway can mitigate this pathway holds potential for curtailing neuroinflammation and preserving cognition [61].

Targeting immune-related pathways, which contribute to neuroinflammation, involves the use of drugs such as anti-inflammatory drugs, antioxidants, as well as those drugs that aim at reinstating the gut microbiome. For example, selective COX-2 inhibitors, proactive drugs blocking the NF- κ B pathway, and probiotics normalizing systemic inflammation have been shown to precondition. Proper immune regulation and a shield against the damaging actions of constant inflammation in the brain are the goals of these approaches.

5.2 Short-chain fatty acids (SCFAs) and their role in brain and immune function

Short-chain fatty acids (SCFAs), particularly butyrate, acetate, and propionate, are metabolic byproducts synthesized by gut bacteria through the fermentation of dietary fiber and resistant starch. These metabolites play a central role in regulating communication between the gut and brain and influence nearly all aspects of neurological activity. SCFAs exert both direct and indirect effects on the central nervous system and thus are critical for overall brain function and behavior [14, 15, 19, 62].

SCFAs contribute to the functional integrity of the hippocampus—an essential region of the brain involved in memory and learning—highlighting the importance of a healthy gut microbiota for overall brain well-being. Butyrate enhances the barrier functions of the blood–brain barrier (BBB) and reduces neuroinflammation, which is essential for neuroplasticity. SCFAs are transported across the BBB through monocarboxylate transporters and help regulate brain function by modulating tight junction proteins such as claudin and occludin, thereby reducing BBB permeability and protecting the brain from inflammation [14, 15, 62, 63].

One of their key mechanisms is the regulation of neuroinflammation. SCFAs control microglial cell function, for example, butyrate reduces the levels of inflammatory cytokines such as IL-1 β , TNF- α , and IL-6, and regulates the M1/M2 phenotype of microglia. These anti-inflammatory actions are partly mediated by the inhibition of histone deacetylase (HDAC), which plays a role in suppressing harmful epigenetic modifications in neurons [63, 64].

At the molecular level, SCFAs modulate neurotransmitter synthesis and neurotrophic factors. Butyrate has been shown to elevate levels of brain-derived neurotrophic factor (BDNF), a molecule essential for synaptic plasticity and memory formation. Additionally, SCFAs influence neurotransmitter pathways by acting on enzymes involved in the synthesis of serotonin, dopamine, and GABA. For instance, acetate and butyrate can upregulate proteins responsible for producing dopamine (*via* tyrosine hydroxylase) and serotonin (*via* tryptophan hydroxylase) [65].

Beyond their neurological roles, SCFAs also have significant effects on immunity. They regulate immune responses and maintain mucosal barrier integrity. These

anti-inflammatory properties are especially relevant because disruptions in SCFA production have been linked to neurodegenerative diseases [66]. The immune and nervous systems interact *via* cytokines, neuropeptides, and neurotransmitters. Dysbiosis in the gut microbiota can alter cytokine profiles, contributing to the development of neuroinflammatory conditions [67, 68]. Immunocytes also synthesize neurotransmitters and neuropeptides that interact with both immune and neural receptors, supporting the concept that immune-activated signaling pathways mediated by SCFAs are integral to gut-brain communication [69].

The human gut microbiota, comprising trillions of microorganisms such as bacteria, fungi, and viruses, performs numerous essential functions, including digestion, vitamin synthesis (e.g., vitamin K and B-complex), immune regulation, and protection against pathogens by competing for nutrients and space [23, 24]. These microbes synthesize bioactive compounds like SCFAs, which affect not only local gut health but also systemic physiological and neurological processes [25].

5.3 Evidence from animal models and human studies

Animal models and human studies investigating the gut-brain axis role in cognition, mood, and memory have increased unprecedentedly. These investigations offer related views on how the microbiota, neurotransmitters, immunologic factors, and molecular communication networks are interrelated and involved in modulating the CNS and behavior.

5.3.1 Animal models

These mouse models include germ-free (GF) mice and specific-pathogen-free (SPF) mice that have played a major role in understanding the societies of gut microbiota in relation to brain health. Ablation of the microbiome results in GF mice with 50% loss of function in learning, memory, and social skills compared to SPF counterparts. For instance, animals in which GF was performed show deficits in hippocampal-dependent tasks, like spatial memory tests using the Morris water maze, and these may be attributed to low levels of BDNF in the hippocampus of GF mice. Depopulation of pathogenic microbial species and the restoration of lost friendly microbes, including *Lactobacillus* and *Bifidobacteria*, enhance learning ability and rewire the brain, proving the complexity of GI microbiota and the human brain [70, 71].

Research with both probiotics and antibiotics in animal, particularly rodent, models also points to the role of the microbiota in cognition. Probiotics have the ability to affect brain functions such as stress coping and memory, HPA axis, and cortisol levels. On the other hand, excess antibiotic use prevents healthy brain development and increases several markers of neuroinflammation, indicating how the gut microbiota affects and is affected by the central nervous system [72, 73].

5.3.2 Human studies

Cross-sectional and intervention human studies have supported those observations from animal studies and provided evidence that microbiota does play a role in cognition and mood. Research focusing on the pathophysiology of the gut-brain connection in IBS and IBD has demonstrated that changes in the composition and/or function of the gut microbiome are linked to compromise in cognitive function and increased stress reactivity [74]. Similarly, the schizophrenic patient and

neuropsychiatric patients who experience depression and anxiety also show signs of gut dysbiosis, reduced serotonin synthesis, and aberrant tryptophan metabolism [75].

Studies with human subjects identified by meta-analysis of dietary interventions and of randomized controlled clinical trials with probiotics sum up well the importance of microbial communities in brain functions. For example, some food products containing *Lactobacillus rhamnosus* and *Bifidobacterium infantis* have been proven to have a positive effect on memory, decrease cortisol levels, and augmentation of the ability to regulate one's emotions. fMRI studies show alteration in the brain connectivity patterns, especially in areas involved in emotional and memory, after probiotic consumption, further extending testimonies on the efforts of microbiota in regulating cognitive functions [76, 77].

6. Link between gut dysbiosis and neurodegenerative diseases

Gut dysbiosis—the imbalance in gut microbiota—has been linked to cognitive impairment and neurodegenerative conditions like Alzheimer's and Parkinson's diseases. A number of studies published recently address the interdependence between the abnormal bacterial composition of gut microbiota and neurodegenerative diseases. The gut-brain connection ensures interaction between the gut flora and the brain, hence impacting neurological health.

6.1 Alzheimer's disease and the gut-brain axis

Cognitive impairment involving amyloid-beta plaque and neuroinflammation in AD has recently highlighted the link between the gut microbiota. Dysbiosis may contribute to AD pathogenesis through:

- *Neuroinflammation*: A disbalance in the gut microbiota induces a systemic inflammation which contributes to neuroinflammation and amyloid-beta accumulation in the brain [78, 79].
- *Microbial metabolites*: These include short-chain fatty acids, which reach the colon and are involved in the regulation of gut and brain barrier function, and are often lower in people with AD. This reduction destabilizes the neurons and their functions [80].
- *Gut barrier integrity*: In dysbiosis-associated “leaky gut,” LPS translocation into the circulation activates Toll-like receptor 4 (TLR4) inflammation [81]. Currently, AD foods/herbal remedy probiotics and dietary modulations in AD are subjects of active research [82].

6.2 Parkinson's disease and gut microbiota

Parkinson's disease is a movement disorder as a result of the degeneration of the dopaminergic neurons in the substantia nigra. Evidence recommends a strong link between gut microbiota and PD:

- *Alpha-synuclein aggregation*: Dysbiosis may facilitate the accumulation of the protein known as alpha-synuclein, a critical feature of PD, in the enteric nervous system before spreading to the brain through the vagus nerve [83].

- *Gut inflammation*: A study tracing ongoing low-grade inflammation of the gut lining due to microbial dysbiosis has also highlighted a link between raised intestinal permeability and systemic inflammation and PD deterioration [84].
- *Bacterial metabolites*: The composition and the function of SCFAs related to gut microbiota changes are linked to the modulation of motor symptoms and neuro-inflammation in PD patients [85]. The use of prebiotics, probiotics, and FMT as a strategy to modulate microbiota may provide positive effects on PD symptoms and possible progression.

6.3 Impact of gut microbiota disruption on memory and cognition

Imbalance in the gut microbiota mainly affects neurological processes such as memory, learning, and executive function. Mechanisms underlying these effects include:

- *Neuroinflammation*: Such inflammation results in alterations of synaptic plasticity and impairment in the hippocampal region that is important for memory [33].
- *Neurotransmitter production*: The microbiome in the gut creates hormones such as serotonin, dopamine, and GABA that have a direct impact on behavior and emotions. Impairment of the synthesis of these molecules causes dysbiosis, resulting in cognitive impairment [86].
- *HPA axis dysregulation*: Stress-induced dysbiosis disrupts the gut-brain-signaling network *via* the activation of the HPA axis, leading to cognitive impairment [87].

These studies emphasize the possibility of interventions for the modulation of the intestinal microbiota, including the use of probiotics and improved diet as means of improving cognitive function and preventing its deterioration [88].

7. Inflammation, stress, and the gut

Chronic inflammation also targets “failed” immune complexes at the blood–brain barrier, which cause significant impairments in memory and cognition, which are associated with chronic inflammation. Elevated levels of pro-inflammatory cytokines, for example, interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF- α), negatively influences neuron growth or neuroplasticity and hampers hippocampal neurogenesis, which consequently hampers cognition. Another of the studies found that elevations in IL-6 over time conferred greater risk of cognitive decline based on population-based data covering 20 years, indicating that, even at early stages, chronic inflammation has adverse effects on memory formation [89].

In addition to that, when there is always peripheral inflammation, microglia in the brain are also activated, which in turn inhibits the differentiation of neuronal stem cells and enhances apoptosis of progenitor neurons. Such a neuroinflammatory cascade disrupts the integration of new neurons developed within specific circuits and leads to memory and learning impairments [90].

As these findings show how stress and inflammation can undermine gut-brain communication, the next section will look at interventions aimed at restoring healthy gut function for better cognitive outcomes.

8. Targeting the gut for cognitive benefits

Given the significant role of gut microbiota in cognitive function, targeted interventions such as probiotics, diet modifications, and microbiome-driven therapies present exciting therapeutic possibilities. Pharmacological intervention through bacterial targeting, known as microbiota modulation, is becoming the focus for non-invasive interventions for neurological and psychiatric diseases. Sequencing techniques have made it possible to arrive at specific probiotics that can supplement one's deficiencies, likely to contribute to poor cognition or mood disorders in the gut microbiome [91]. The best-known subcategory of the probiotics is psychobiotics that act on and modulate the microbiota's bidirectional communication with the brain for improving mental health, while *Lactobacillus rhamnosus* influences the stress level and even memory stress of animals in studies conducted without using humans. Finally, postbiotics, which are products of bacterial metabolism, including SCFAs, have beneficial effects, including enhancement of the integrity of the blood–brain barrier and reduction of inflammation. These findings suggest that this approach is especially viable in neurodegenerative diseases such as Alzheimer's and Parkinson's due to a disruption of gut bacteria before the onset of symptoms. These therapies focus on the microbiome, which, if modulated, can help slow down the progression of illness through a decrease in neuroinflammation and enhanced communication between gut and brain [92].

9. Pharmacological approaches targeting gut-brain pathways

Building on the potential of gut-targeted therapies, pharmacological approaches have been developed to modulate the gut-brain axis, aiming to improve memory and cognitive processes. Pharmacological practices have been targeted at the physiological ways in which signaling interactions between the gut and the brain can promote improved memory and simpler cognitive processes, as shown in **Table 1**.

Strategy	Description	Key references
Targeting microbial metabolites	Substances that promote the synthesis of beneficial gut-derived metabolites, particularly short-chain fatty acids (SCFAs). These compounds are linked to decreased neuroinflammation and enhanced synaptic plasticity.	Frost et al. [93]
Receptor modulation	Medications acting on receptors that influence gut-brain communication, especially those affecting GI motility and cognition. Example: SSRIs target serotonin receptors in the GI tract.	Mayer et al. [33] Guzel and Mirowska-Guzel [94]
Psychobiotics development	Use of psychobiotics—a subclass of probiotics with psychopharmacological effects—to treat mood and cognitive disorders <i>via</i> gut microbiota regulation. Recent research has highlighted advances in quantifying bioactive microbial metabolites (e.g., SCFAs, GABA) that mediate gut-brain effects and supports their relevance for mental health intervention strategies.	Dinan et al. [95] Kyei-Baffour et al. [96]

Table 1.
Therapeutic strategies.

10. The microbiome's role in aging and longevity

As we explore the potential of gut-targeted therapies, it is also important to consider the role of the gut microbiota in aging and cognitive decline. The natural biological phenomenon in senescence comprises not only the gradual physical deterioration but also the various forms of cognitive constraints, for example, memory deterioration and poor control of executive functions, and a decrease in the speed of mental processes. Recent studies have established that the armies of trillions of microbes living in the gut, known as the gut microbiota, dynamically regulate these processes of aging. During aging, they found that the microbial and inflammatory properties grew more prevalent, and there was a lesser presence of various beneficial microbes such as *Bifidobacteria* and *Akkermansia muciniphila* [97]. These alterations modify the immune system, thereby promoting inflammation, which increases neuroinflammation, which is a major trigger to cognitive decline.

11. Conclusion

The gut-brain axis is a remarkable connection that maps the gastrointestinal tract and the brain and underlines the influence of gut microbiota on the brain and cognition. The gut microbiota can influence neurotransmitter synthesis, immune regulation, and synthesis of SCFAs and subsequently contribute to the modulation of synapse plasticity, neuroinflammation, and cognition with special reference to learning and memory phenomena.

Intestinal dysbiosis has emerged as a critical factor co-related with cognitive impairment, Alzheimer's and Parkinson's diseases, and mood disorders. The approach to gut health by management of diet, probiotics, and drugs indicates potential to boost brain health and control neuroinflammatory disorders. These therapies focus on how essential it is to preserve microbial richness and composition in the bowels for cognitive preservation and superior mental health.

Further research in this area has the ability to change the way patients with cognitive and neurodegenerative disorders are treated, as well as expand knowledge of how the brain and its biome are intricately dependent on each other.

Abbreviations

ENS	enteric nervous system
CNS	central nervous system
GABA	gamma-aminobutyric acid
SCFAs	short-chain fatty acids
HPA	hypothalamic–pituitary–adrenal (axis)
GIT	gastrointestinal tract
BBB	blood–brain barrier
LTP	long-term potentiation
LTD	long-term depression
IBS	irritable bowel syndrome
IBD	inflammatory bowel disease
CCK	cholecystokinin
GLP-1	glucagon-like peptide 1

PYY	peptide tyrosine-tyrosine
fMRI	functional magnetic resonance imaging
GERD	gastroesophageal reflux disease
DRG	dorsal root ganglia
ROS	reactive oxygen species
MSNs	medium spiny neurons
AMPA	α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor
CB1	cannabinoid receptor type 1

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