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# From Gut to Brain: How Microbiota Modulate Stress and Mental Health

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**ABSTRACT:** The microbiome is a collaborating microbial community that refers to the collection of microorganisms, their structural substances, genes, and metabolites that exist in a habitat, creating a separate community in many places, such as the human gut. They form a complex ecosystem that helps in homeostasis, digestion, nutrient uptake, energy production, vitamin synthesis, and immune and inflammatory modulation. They change in response to a variety of environmental factors, like exercise, diet, and medication. Dysbiosis, or microbiota imbalances, affects body functions and leads to a variety of diseases, making it an important area for management. Chronic abdominal symptoms are recently regarded as a dysregulation of the interactions between the gut, gut microbiome, enteric nervous system, and central nervous system; the gut-brain pathways, thereby affecting the patient's behavior and attitude. In addition, the gut microbiota produces about 90% of serotonin. Therefore, dysbiosis of gut microbiota leads to cognitive and mood disorders. Chronic stress activates the brain to produce stress hormones that influence the gut microbiota, affecting gut peristalsis and intestinal permeability, which creates a hostile environment for beneficial microbiota, allowing the stress-resistant species to dominate. Moreover, it decreases the formation of essential metabolites such as short-chain fatty acids (SCFAs), which regulate inflammation and mood, increasing depression and anxiety, and leads to further stress and negative feedback, producing more vicious cycles.

## INTRODUCTION

The Microbiota refers to the entire community of living microorganisms, composed of bacteria, fungi, viruses, protozoa, and archaea, inhabiting a defined environment; living in and on the human body since birth, transferred vertically through generations (Attiq et al., 2024). The microbiome is an interactive microbial community that refers to the entire collection of such microorganisms, their genes, gene products, structural elements, and metabolites produced by microbial activities, that exist in particular environmental niches within a habitat, forming distinct communities in places like the human gut, skin, lung,

and oral cavity (Fig. 1). The human microbiota, also known as "the hidden organ," contributes over 150 times more genetic information than that of the entire human genome (Berg et al., 2020).

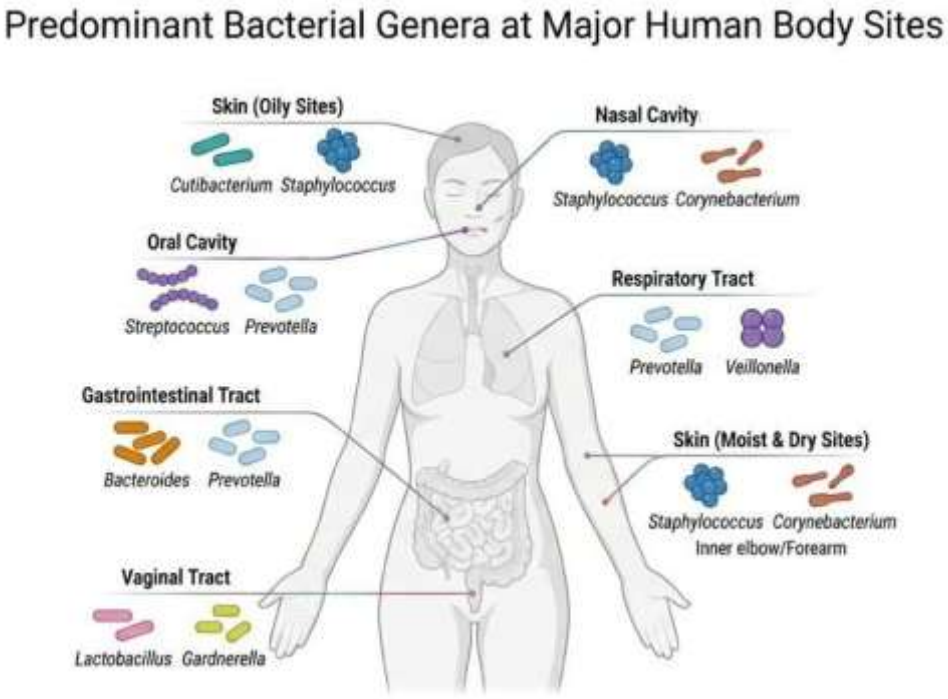


**Figure. 1:** Anatomical Distribution of Predominant Bacterial Genera Across Major Human Microbiota Niches. Schematic overview illustrating the top two codominant bacterial genera characterizing the healthy human microbiota at specific physiological sites, including the gastrointestinal tract, respiratory, oral cavity, vaginal tract, and distinct cutaneous microenvironments.

These microbial communities are in symbiosis with the host; they form a complex ecosystem that is crucial for health, contributing to homeostasis via aiding digestion, developing & regulating immune functions, and protecting against pathogens. Moreover, they are diverse, dynamic and change in response to a variety of environmental factors, including exercise, diet, medication and other exposures, However, microbiota imbalances, known as dysbiosis, result in dysregulation of body functions, ending up with diseases including diabetes, cardiovascular, respiratory, neurological, autoimmune disorders and cancers, making it a key area for diagnostics and therapeutic interventions (Hou et al., 2022).

**Composition of Human Microbiota**

The composition of human microbiota varies from site to site. Human microbiota consists of 10-100 trillion microorganisms, accounting for approximately 1-3 % of the body mass. This number is 10 times the number of human cells, which comprises over 150 times more genes than the human genome (O'Hara & Shanahan, 2006). Meanwhile, there exists significant variation at higher taxonomic levels (Leviatan et al., 2022). However, despite this diversity, certain core microbial species are present across a large portion of the population, suggesting a common set of functions essential for human health (Lozupone et al. 2012).

**The gut microbiota**

Gut microbiota is considered the most significant one in maintaining human body health. A healthy gut microbiota is characterized by a diverse and balanced community of microorganisms that perform vital functions for the host (Leviatan et al., 2022). Taxonomically, bacteria are classified according to phyla, classes, orders, families, genera, and species. Gut microbial flora consists of bacteria from the four phyla, namely, Firmicutes, Bacteroidetes, Actinobacteria, and Proteobacteria, with a lower proportion of the latter two (Ley et al., 2007). Anaerobes such as Bifidobacterium, Clostridium, Bacteroides, and Eubacteria, and aerobic bacteria including Escherichia, Enterococcus, Streptococcus, and Klebsiella constitute the majority of

gut microbiota and contribute to its diversity (Eckburg et al., 2005). The most studied fungi (gut mycobiota) are Candida, Saccharomyces, Malassezia, and Cladosporium (Auchtung et al., 2018). In addition to bacteria and fungi, the human gut microbiota also contains viruses, phages, and archaea, mainly M. smithii (Lozupone et al. 2012).

Gut microbiota varies in different anatomical parts of the GI tract. For example, Proteobacteria such as Enterobacteriaceae are found in the small intestine but not the colon. Meanwhile, Bacteriodetes such as Bacteroidaceae, Prevotellaceae, and Rikenellaceae are often found in the colon (Flint et al., 2012). Such variations are mainly due to the different environments. In the small intestine, the transit time is short, and bile concentration is high, while in the colon, which has slower flow rates and milder pH, larger microbial communities, especially anaerobic types, are commonly observed (Milani et al., 2017).

In healthy conditions, the gut microbiota exhibits stability, resilience, and symbiotic interaction with the host. There is a lot of research into the definition of a "healthy" gut microbiota and its link to host physiological functions. A healthy microbiota community often demonstrates high taxonomic diversity, high microbial gene richness, and stable core microbiota (Fan & Pedersen, 2021). A healthy gut is defined as not only 'free from diagnosed diseases' but also 'operates without causing any discomfort or signs of dysfunction'. This definition implicitly relies on a well-balanced gut microbiota, because imbalances often lead to symptoms, like bloating, gas, irregular bowel movements, and discomfort (Hul MV et al., 2024).

The relative abundance of certain bacterial genera at lower taxonomic levels could be a more precise indicator of gut health. For instance, a higher prevalence of genera such as Bifidobacterium and Lactobacillus is often associated with beneficial gut functions, including improved digestion and enhanced immune response; whereas an over-representation of genera like Clostridium or Escherichia can be indicative of a microbiota deviation and associated with GI disorders, such as Irritable Bowel Syndrome (IBS) or Inflammatory Bowel Disease (IBD). IBD is classified into Crohn's Disease and Ulcerative Colitis. It has been suggested that there is a significant correlation between the development of IBD and alterations in the gut microbiome (Kaur & Raman Thakur, 2025). However, some significant limitations and counterexamples challenge the reliability of these indicators. For example, an overgrowth of Lactobacillus can contribute to conditions such as Small Intestinal Bacterial Overgrowth (SIBO) (Li et al., 2021).

**Individual variations in gut microbiota**

The composition of gut microbiota is influenced by a complex interplay of both intrinsic (host) and extrinsic (external-environmental) factors, which significantly impact human health. Host-related factors encompass age and delivery mode, liver metabolic capacities, immune system functionality, production of specific bioactive lipids, stomach acidity, bile acid production, gut motility, oxygen levels, and biological factors, including mucus production. Genetic variations also contribute to determining microbial diversity and resilience, influencing disease susceptibility and treatment responses (Inchingolo et al. 2024) & (Mohanty et al., 2024). External factors, including dietary habits, hygiene practices, exposure to pollutants and chemicals, psychological stress, and lifestyle elements such as physical activity, sleep patterns, and social interactions, also play crucial roles in shaping the microbial landscape (Winter & Bäumler, 2023). Thus, a person might not have a diagnosed GI disorder but still experience "suboptimal" gut health due to an imbalance in the microbial structure and function, poor dietary habits, stress, or other lifestyle factors. This perspective highlights the critical balance and interplay between the gut's physical structure, its operational functions, and the complex community of microbes that it harbors (Fassarella et al., 2021).

**Development of Gut Microbiota Early in Life**

The fetal gut is sterile; infants develop within a relatively sterile environment in utero. However, microbial colonization rapidly starts during the birth process, influenced by various factors including the mode of delivery, maternal health, breastfeeding, and early antibiotic exposure. Many of the early gut colonizers originate from the mother, with the mode of delivery significantly influencing the gut microbiota of term infants in their early life (Ley et al., 2006).

Vaginally-delivered infants acquire microbiota resembling the maternal vaginal and gut microbiota, initially dominated by Lactobacillus with Senathia and Prevotella also present (Yao et al., 2021). In contrast, infants born via caesarean section exhibit lower microbial diversity, acquiring microbes that resemble maternal skin flora, such as Staphylococcus and Propionibacterium. Vertical transmission is crucial for maternally-acquired bacteria such as Bifidobacteria, whereas horizontal transmission from environmental exposures is more relevant for spore-forming taxa like Clostridia (Altmann et al., 2016).

Breast-fed infants have higher levels of Bifidobacterium compared to formula-fed infants, leading to a more acidic intestinal environment. This reduction in gut pH may serve as a defense against pathogens. Breastfeeding is the single most significant factor in shaping the infant gut microbiome, as it supplies beneficial bacteria like Bifidobacterium with human milk oligosaccharides (HMOs), which selectively promote the growth of these bacteria and play a crucial role in early gut health. Formula-fed infants have a different microbiota profile, with lower levels of Bifidobacteria, which can affect immune development and increase susceptibility to diseases such as allergies and asthma (Hoskinson et al.,2023).

Immediately after birth, colonization continues to change depending on various factors such as diet, environment, and medications. The infant gut microbiome develops in three stages: a developmental phase (3–14 months) influenced by birth mode and feeding, and a transitional phase (15–30 months) with shifts associated with the introduction of different solid foods. In the stable phase (31–46 months at approximately the age of 3–4 years), the microbiome resembles an adult configuration, where the children's gut microbiota becomes comparable to that of adults, with three major microbial phyla, including Firmicutes, Bacteroidetes, and Actinobacteria, becoming dominant (Fouhy et al., 2019). However, the gut microbiome may undergo a more prolonged development, resulting in a composition that is as distinctive as a set of fingerprints (Hollister et al., 2015). Subsequently, at an older age, dietary and immune system changes potentially have an impact on the composition of the human gut microbiota. Specifically, older people tend to exhibit decreased Bifidobacterium and increased Clostridium and Proteobacteria. The decrease in the anaerobic bacteria Bifidobacterium contributes to deteriorated inflammatory status due to its role in stimulating the immune system (Guigoz et al., 2008).

**Functions of Gut Microbiota**

Gut microbial balance is closely relevant to human health and diseases. The gut microbiota performs several key functions essential for maintaining host health. The microorganisms in the GI tract play a critical role in digestion, nutrient uptake, energy harvest, vitamin synthesis, inflammatory modulation, and host immune status (Theis et al., 2025). The microbiota competes with pathogenic microbes for resources and space, thereby preventing their colonization and potential invasion. Gut microbiota produces a variety of bioactive compounds, including Short-Chain Fatty Acids (SCFAs), which exert anti-inflammatory effects and contribute to the integrity of the gut barrier. Moreover, it is closely involved in nutrient extraction as it aids in the digestion of complex carbohydrates and synthesizes essential vitamins. Additionally, current advances have shown that human microbiota is closely involved in the regulation of the immune system (14- Fan & Pederson, 2021).

**PROTECTIVE ROLE OF GUT MICROBIOTA**

The gut microbiota and the gut barrier represent critical lines of defense that work synergistically to protect the host from harmful environmental influences. Maintenance of a symbiotic relationship promotes homeostatic balance, which allows the growth of beneficial microbes and prevents the overgrowth of pathogenic microbes (Shemtov et al., 2023).

Probably due to the necessity of competing with foreign bacteria, gut bacteria have developed various mechanisms of suppressing competitors, including the secretion of diverse bacteriocins (Pukatzki et al., 2006). A contact-dependent competition in the gut, namely "Type 6 Secretion System", was originally identified in the bacterial secretion system involved with eukaryotic cells, which was later found relevant to intra-species killing. Besides the type 6 system, other systems such as "Type 7" (or ESX system) also mediate the intra- and inter-species killing (Whitney et al., 2017).

The intestinal mucosal barrier not only provides protection by preventing microbial contact with intestinal epithelial cells, but also provides the microbes with nutrients in the form of secreted glycoproteins (Kim & Ho, 2010). Metabolites generated by the microbes activate receptors such as Toll-like receptors (TLRs) and Nucleotide-binding and Oligomerization Domains (NOD) like receptors (NLRs). Activation of these receptors can induce the signaling pathways essential for promoting mucosal barrier function and preventing gut inflammation (Macpherson & Uhr, 2004).

Gut Microbiota also produce mucin glycoproteins, antimicrobial peptides, and local secretory IgA immunoglobulins, whilst serving as signaling molecules. These mechanisms prevent the translocation of the gut microbiota from the intestinal lumen to the circulation and build up gut immunity. Such immune modulation can therefore be used to design treatment strategies against various diseases by targeting various signaling pathways (Schroeder & Bäckhed, 2016).

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**Metabolic Role of Gut Microbiota**

A critical role of the microbiome lies in its profound influence on host metabolism including the metabolism of energy substrates, xenobiotics, synthesis of micronutrients like vitamins, and modulation of host immune defenses through the release of gut hormones such as Cholecystokinin, Glucagon-Like Peptide, and the Peptide YY (Jyoti & Priyankar Dey, 2025).

**Energy Metabolism**

For energy and nutrient extraction from food, microbiota play crucial roles due to the versatile metabolic genes, which provide independent, unique enzymes and biochemical pathways. Metabolic function of the microbes depends on the fermentation of dietary carbohydrates that escape digestion (in the form of resistant starch, non-starchy polysaccharides, and oligosaccharides). Such fermentation produces beneficial metabolites such as Short-Chain Fatty Acids (SCFAs), mainly acetate, propionate, and butyrate, all of which are energy sources for the host intestinal epithelium (Peled & Livney, 2021). The Short-Chain Fatty Acids can be quickly oxidized to release high-energy molecules like Acetyl-CoA that participate in metabolic pathways and generate energy in the form of Adenosine Triphosphate (ATP) (Portincasa, P. et al. 2022).

The GI tract digests sugars from foods. Metabolizing polysaccharides requires multiple enzymes produced by various bacteria. For example, members of Bacteroides express enzymes like transferases, hydrolases, and lyases that participate in carbohydrate metabolism, and modulate the activity of host lipid- degrading enzymes like lipoprotein lipase (Ramakrishna, 2013). Similarly, the microbial members of the gut metabolize dietary and endogenous (non-dietary) proteins via microbial proteinases and peptidases, along with host proteinases, as they facilitate protein digestion and absorption (Rodríguez-Romero et al., 2022). Pathogenic Enterobacteriaceae utilizes sugar and amino acids in gut. These nitrogenous substrates can be used for energy production (i.e., through fermentative pathways) or for biosynthesis, where gut bacteria act as a source of essential amino acids such as lysine and threonine through de novo synthesis that contributes to amino acid homeostasis in the host (Metges, 2000).

**Role of Gut Microbiota in Xenobiotic Metabolism**

Microbes inhabiting the intestinal tract of humans represent a site for xenobiotic metabolism. The gut microbiome can alter the metabolic outcome of Xenobiotics; these are substances that are not native to the host, such as pharmaceuticals, drugs, chemicals, food additives, environmental toxicants, and heavy metals, thereby changing their pharmacokinetics and pharmacodynamics (Collins & Patterson, 2020). The mechanism involves direct chemical modification of xenobiotics by the gut microbiome and converting chemicals or drugs into inactive metabolites, either through the intestinal tract or re-entering the gut via enterohepatic circulation. This results in increased metabolism or bio-activation, depending on the enzymatic activity within the microbial niche. Alternatively, the microbiome can alter the absorption of drugs and indirectly change their pharmacokinetics and pharmacodynamics by modulating the gene expression of host metabolic enzymes, including cytochrome P450, transporters, and other conjugative enzymes (Maurice et al., 2013). Studies have identified bacterial genes of gut microbes to metabolize several drugs, such as Levodopa used to treat Parkinson's disease, and Levamisole used for parasitic infections (Zimmermann et al., 2019).

**Role of Gut Microbiota in Vitamin Synthesis**

Besides providing an energy source for host cells, microbes are an excellent endogenous source of micronutrients like vitamins. Vitamins synthesized by gut commensal microbes include water-soluble B vitamins such as biotin, riboflavin, folate, thiamine, pantothenic acid, and fat-soluble Vitamin K, all of which can be utilized by the host cells and are crucial for host metabolism, immunity, cell function, and blood clotting, with B vitamins supporting energy and Vitamin K being critical for the activation of clotting factors and also works as a free radical scavenger to protect our cells from oxidative damage (LeBlanc et al., 2013). B Vitamins include a group of water-soluble essential nutrients that serve as precursors of essential cofactors in numerous metabolic pathways, critical in energy metabolism, and serve as coenzymes in various redox reactions. Gut bacteria that are capable of synthesizing and supplying an excessive amount of vitamin B for the host, as well as other intestinal microbes, are known as vitamin B-producers (Wan et al., 2022). The importance of having a healthy gut microbiome is crucial as an endogenous source of vitamins, because the human body lacks the biosynthesis machinery to synthesize most vitamins and therefore relies on exogenous dietary sources (Pham et al., 2021).

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## ROLE OF GUT MICROBIOTA IN IMMUNE MODULATION

Microbial communities within the gut microbiome, form intricate relationships with the human host, encompassing both symbiotic and parasitic interactions, which play essential roles in regulation of host metabolic responses, epithelial barrier function and profoundly influence the host's immune system, through immune education and immune regulation, especially early in life (Delzenne et al., 2024). A well-balanced gut microbiome, conferring constant interaction with the host immune system, is essential for health. The human microbiota not only protects the host from external pathogens by producing antimicrobial substances, but also serves as a significant component in the development of intestinal mucosal integrity, as well as the development and modulation of gut immunity (Clemente et al., 2012). The gut microbiome and the immune system are in constant communication. A large body of evidence suggests that the immune system is educated by the microbiota in a temporally restricted manner, widely recognized as the "window of opportunity" (Ignacio et al., 2024). While the foundation of the immune system begins before birth, a growing body of literature indicates that signals from the maternal microbiota can influence the fetal immune system development in utero. In early life, the gut microbiota plays a key role in the development and maturation of the immune system. Gut colonization begins at birth, where the gut microbiome establishes itself in a newborn's sterile gut, playing a critical role in the maturation of the host immune system and immune responses (Fernandes & Lim, 2024).

Infants begin life with a simple yet variable microbial community. During the first three years of life, the infant microbiota undergoes dynamic changes and ultimately stabilizes into an adult-like gut environment, equipping the host with immunity. While an adult-like microbial composition begins to emerge around one year of age, a stable community similar to that of adults is typically established by 3 years (Mogoş et al., 2025). Hence, during the early years of life, when the immune system is still immature, as well as the limited immune memory, increases the newborn's vulnerability to infectious agents. Infants become highly susceptible to infectious pathogens that can result in disease states like allergies, autoimmune, and inflammatory disorders. Dysbiosis of the microbiome during this critical early period in development is associated with increased susceptibility to both acute and chronic immune-mediated diseases (Chu et al., 2023).

While the innate and adaptive responses of an immature immune system result in high susceptibility to infections, it also favors the immune-regulatory establishment of microbiota without a severe inflammatory response. This necessitates a fine adjustment between establishing tolerance towards the commensal microbiota and preserving inflammatory responses against pathogenic invaders. This "window of opportunity" in early life is thought to be crucial for the proper development of the immune system, setting the tone of subsequent immune responses in adulthood and modulating the risk of developing chronic and metabolic inflammatory diseases (Ignacio et al., 2024).

On formulating and testing the hypotheses on the functional development of the immune system, the transition from neonatal to adult immunity, encompassing a series of non-redundant temporally controlled events that may be dependent on each other to establish immune homeostasis, must be considered. This phenomenon, named "layered immunity" (Herzenberg and Herzenberg, 1989), might explain why significant differences in immunity between newborns and adults exist to establish homeostasis during the early postnatal period (Hornef & Torow, 2020). In this early period, when mucosal barriers may not be fully developed, interactions between innate immune cells and foreign antigens help to shape adaptive immune responses, influencing the newborn's ability to mount effective responses later in life (Hornef & Torow, 2020). Postnatally, the window of opportunity confers a period in early life, where pronounced synergistic changes are observed in the microbiota composition and the host's immune system development. Gut colonization begins with a low number and diversity of microbes; simultaneously, the early-life mucosal innate immune system appropriately recognizes the presence of commensal bacteria via Pattern Recognition Receptors (PRRs), which detect specific, conserved molecular structures on pathogens known as Pathogen-Associated Molecular Patterns (PAMPs). Toll-Like Receptors (TLRs), found in epithelial cells, represent a major class of PRRs, including TLR2, TLR4, TLR5, and TLR9, which recognize various bacterial cell components, like lipopolysaccharides (LPS), flagellin, and lipoproteins (Jing et al., 2025).

Expression of TLR5 is high in intestinal epithelial cells (IECs) of infant mice to limit early-life colonization by bacteria that express flagellin, a hallmark of many pathogenic bacteria, which is then downregulated in adulthood (Fulde et al., 2018). During the neonatal period, persistent but low-grade signaling through Toll-like receptor (TLR) 4 in the murine epithelium is crucial to induce tolerance and avoid exacerbated inflammation upon postnatal colonization (Chassin et al., 2010). Bifidobacteria generate exopolysaccharides that have significant effects on host immune responses, mediated in part by TLR-2 and C-type Lectin

Receptors (Schiavi et al., 2018). Exposure to lipopolysaccharides shortly after birth triggers a signaling process in intestinal epithelial cells (IECs) that increases the production of the IL-1 Receptor-Associated Kinase 1 (IRAK1) Protein, protecting the cells from damage caused by bacteria. This protective effect leads to a reduced response to later TLR stimulation, promoting microbial colonization and helping maintain a balanced relationship between the host and its microbes (Leavy, 2010). Thus, PRRs facilitate communication between the body and gut bacteria, fostering the establishment of tolerance, selection of microbial members, and reducing the likelihood of overreacting to microbes, thus preventing adverse inflammation, while concomitantly generating rapid effector responses against infectious challenges (Fulde et al., 2018). Therefore, critical early life interactions between the host immunity and microbiota are important to the establishment and maintenance of immune homeostasis and may impact susceptibility to infections and diseases later in life (Dimri and Rizzo, 2022).

It is important to note that soluble factors, like maternal antibodies, transferred across the placenta and delivered via breast milk, protect against neonatal infection and inappropriate immune activation by the microbiota during the postnatal period. This passive immunity provided by the mother lasts only 6 months after birth in humans. During this time, the newborn's cellular immune system matures rapidly alongside the development of their microbiome (Qi et al., 2012). Literature affirms the association of microbial colonization with protective Immunoglobulin A (IgA) antibody production, that in-turn confers humoral immunity and mediates innate lymphoid cells' activation, mirroring the phenotype and function of T-cells, and other immunomodulatory effector cells (Lisicka et al., 2025). Various cytokines secreted by these cells also play an important role in early immune response to allergens, bacterial, and parasitic infections. Microbial interaction with the host immune cells initiates the production of pro-inflammatory cytokines that can reach the brain via blood circulation and alter brain function (Raso et al., 2023).

Gut microbes influence the activity of the immune defense mechanisms through modulation of the activity of the immune cells (B cells, T-cells, myeloid cells, Innate Lymphoid Cell (ILC) (Hou et al., 2022). At birth, adaptive immunity in the intestine is mainly conferred by thymus-derived T cells exhibiting an innate-like function, which are then replaced by antigen-experienced effector T lymphocytes, and by maternal secretory IgA, transferred through the milk, which decreases over time and is replaced by endogenous IgA production with the maturation of plasma cells. The temporal regulation of the mucosal immune system is believed to be crucial for determining the threshold of immunological responses later in life (Ignacio et al., 2024).

Certain populations of T cells, termed unconventional T cells, seed various body tissues in response to early life developmental cues and antigen exposure. In contrast to conventional T cells, which display immense receptor diversity, unconventional T cells express semi-invariant T cell receptors (TCRs) that limit their antigenic range, similar to innate immune receptors. One such population is the invariant Natural Killer T (iNKT) cells, which express an invariant TCRα chain and are restricted by CD1d. iNKT cells are present in human mucosal tissues and participate in the control of tissue homeostasis and inflammation (Constantinides and Belkaid, 2021). This interaction is a delicate balance, as imbalances in T-cell activity can lead to a range of health issues, including inflammatory and autoimmune diseases (Ivanov et al. 2022).

Microbial-derived metabolites are integral components of immune functions' maturation, which are crucial for host health and survival, due to their significant role in maintaining gut barrier integrity and modulating immune responses. Increasingly, the role of bacterial metabolites in shaping host immune function is being recognized (Losol et al., 2024). Before birth, bacteria-derived metabolites, released by maternal microbiota, can cross the placenta and reach the fetus, inducing the expansion of Innate Lymphoid Cells (ILCs) and intestinal Mononuclear Cells (iMNCs) in the intestine of the newborn (Kim et al., 2025). Importantly, many immune-regulatory bacterial metabolites are generated from dietary ingredients (e.g., fiber, tryptophan), linking diet and lifestyle to immune health via microbial mechanisms. Changes in dietary habits and microbiota composition would result in reduced levels of immune-regulatory metabolites, hardwired into immune cell development and decision-making processes, that contribute to increased risk of inflammatory disease throughout the lifespan (Canani et al., 2024). As environmental cues, bacterially-derived metabolites are crucial for modulating the immune system, particularly the function of the epithelial barrier and mucosal immune cells (Su et al., 2022). These metabolites are regarded as messengers from the gut microbiota, since bacteria are capable of producing unique molecules that humans cannot, and it is worth mentioning that many immune cells in the intestine express receptors for these molecules (Takeuchi et al., 2024). The most common microbial metabolites are SCFAs, Tryptophan derivatives, Secondary Bile Acids (BAs), Histamine, Sphingolipids (SLs), and Polyamines (Losol et al., 2024).

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**Short Chain Fatty Acids (SCFAs)**

Bacteria directly produce Short Chain Fatty Acids (SCFAs) through the fermentation of complex carbohydrates typically found in dietary fibers. Intestinal SCFAs mainly include acetate, propionate, butyrate, and valerate. SCFAs have been extensively studied due to their pivotal roles in intestinal homeostasis; maintaining gut barrier integrity, modulating immune responses, and serving as an energy source for colonic cells (de Vos et al. 2022). SCFAs are critically important for the establishment of immune-tolerogenic networks. Specific G-Protein Coupled receptors (GPCRs) are activated by SCFAs, resulting in improved regulation of both innate and adaptive immune responses. Through the effects on many cell types, SCFAs exert an array of regulatory effects that are important for preventing inflammatory diseases (Sasaki et al., 2024). Moreover, propionate and butyrate can activate the Peroxisome Proliferator-Activated Receptor γ (PPARγ), a crucial nuclear receptor and transcription factor that regulates numerous genes involved in energy metabolism, inflammation, cell differentiation (especially fat cells), and apoptosis. Activated by SCFAs, PPARγ plays significant roles in insulin sensitivity, adipocyte function, immune response, and diseases like diabetes, obesity, and certain cancers, acting as a master regulator in many cell types (Hou et al., 2019). A health-promoting role for butyrate has been identified. It regulates the plasticity of type 3 innate lymphoid cells (ILC3) and enhances interleukin-22 (IL-22) production (Yang et al. 2020).

Butyrate also plays a significant role in modulating adaptive immunity. Butyrate influences the differentiation of B cells and plasma cells, promoting the production of intestinal IgA. During the differentiation of regulatory T (Treg) cells, butyrate supports the expression of FOXP3 and the secretion of IL-10. Moreover, it shifts the balance between T helper 1 (TH1) cells and TH17 cells by upregulating T-bet expression and downregulating RORγt expression. These are master transcription factors that define T helper (Th) cell lineages, with T-bet driving Th1 cells (producing IFN-gamma) and RORγt defining Th17 cells (producing IL-17). (Dupraz et al. 2021).

**TRYPTOPHAN**

Tryptophan-derived metabolites such as indole and Indole-3 Lactate are produced by a variety of gut microbes. Many of these tryptophan metabolites are ligands for the Aryl hydrocarbon receptor (AhR). AhR signaling is considered a key component of various immune processes at barrier sites that are crucial for intestinal homeostasis. These include effects on epithelial function, barrier integrity, and many immune cell types, such as intraepithelial lymphocytes, T Helper 17 cells, T Helper 22 cells, T regulatory cells, Innate Lymphoid Cells, Macrophages, Dendritic Cells, and Neutrophils. In addition, Indoles were shown to regulate intestinal barrier function via enhancing IL-10 receptor (IL-10R) expression and activation of the Toll-like receptor 4 (TLR-4) (Yu et al., 2018).

**Secondary Bile Acids (BAs)**

Secondary BAs, including deoxycholic acid (DCA) and lithocholic acid (LCA), are generated in the intestine following bacteria-mediated transformation from primary BAs. These secondary BAs can signal via multiple receptors that are expressed by a diverse range of innate and adaptive immune cells, which modulate their differentiation and function (Su et al., 2023).

**Histamine**

Following decarboxylation of histidine, histamine can be secreted by several bacteria. Bacterial-derived histamine is immunologically active, it influences both innate and adaptive immune responses via binding to four different receptors, namely histamine receptor 1–4 (H 1-4 R). Dendritic Cells (DCs) exposed to histamine have been shown to increase their antigen-presenting capacity and Th1 polarization via H1R. Histamine secretion by microbes in the gut influences cytokine responses in the gut, activation of H2R on DCs drives IL-10 secretion, and a decrease of IL-12 secretion (Ferstl et al., 2017). Histamine secretion by microbes in the gut reduces respiratory allergic inflammation in murine models. In addition to effects on the innate immune system, T cell polarization and cytokine release are also influenced by histamine stimulation via different HRs (Barcik et al., 2019).

**Sphingolipids (SLs)**

SLs are a class of membrane lipids that serve as vital structural and signaling bioactive molecules in organisms originating from both host cells and the gut microbiota. SLs can influence gut immune homeostasis positively or negatively, via effects on intracellular calcium levels, cell motility, apoptosis, cell growth, and migration, and attenuating inflammatory responses (Lee et al., 2023).

**Polyamines**

Polyamines are compounds with amino groups at both ends of a hydrocarbon, which can be produced by host cells and a wide variety of gut microbes. Polyamines play a crucial role in many fundamental biological functions, including gene regulation, stress resistance, cell growth, proliferation, and differentiation, and are associated with both eukaryotic and prokaryotic cells in health and disease, as they can impact mucosal allergic inflammation (Nakanishi & Cleveland, 2021).

The lack of immune regulatory molecules (released from microbiome), potentially coupled with excess pro-inflammatory mediators, results in a poorly-regulated, hypersensitive immune system that reacts inappropriately to non-pathogenic stimuli and contributes to increased risk of inflammatory disease throughout the lifespan (Hitch et al., 2022).

**THE GUT-BRAIN-AXIS**

Recent studies have documented the bidirectional interactions between the gut and the brain. Communication among the brain, gut, and gut microbiome involves multiple feedback circuits, with numerous pathways and interactions among these loops (Wang et al., 2023). The shift from "single-organ management" to "axis-based link control" represents a standard transition that has exposed innovative modalities for the prevention and treatment of multiple diseases (Loh et al., 2024). Changes in gut-brain interactions play a key role in gastrointestinal diseases (Osadchiy et al., 2019). Understanding the pathogenesis of gut-brain disorders and the relative involvement of peripheral and central approaches has emerged. Novel research has focused on the effective treatment of complex diseases, including those involving the gut-brain axis (Caldarelli et al., 2024). The pathology of chronic abdominal symptoms is regarded as a dysregulation of the interactions between the gut, gut microbiome, enteric nervous system, and central nervous system (Dicks 2023; Griffiths et al., 2024; He et al., 2024). These alterations led to local gastrointestinal disorders that affected gut motility and secretions, modulated local immune responses and epithelial turnover and repair, and impacted the central nervous system, thereby affecting the patient's behavior and mood (Figure 2) (Mayer et al., 2022). This novel view has been endorsed for multiple pathophysiological brain disorders that were previously thought to be limited to the central nervous system. Accumulating preclinical and clinical investigations have observed that disorders of gut microbiota are strictly associated with various psychiatric disorders such as anxiety and depression, neurological conditions like autism spectrum condition, Alzheimer's, and Parkinson's diseases (Liu et al., 2023; Xu and Lu, 2025).

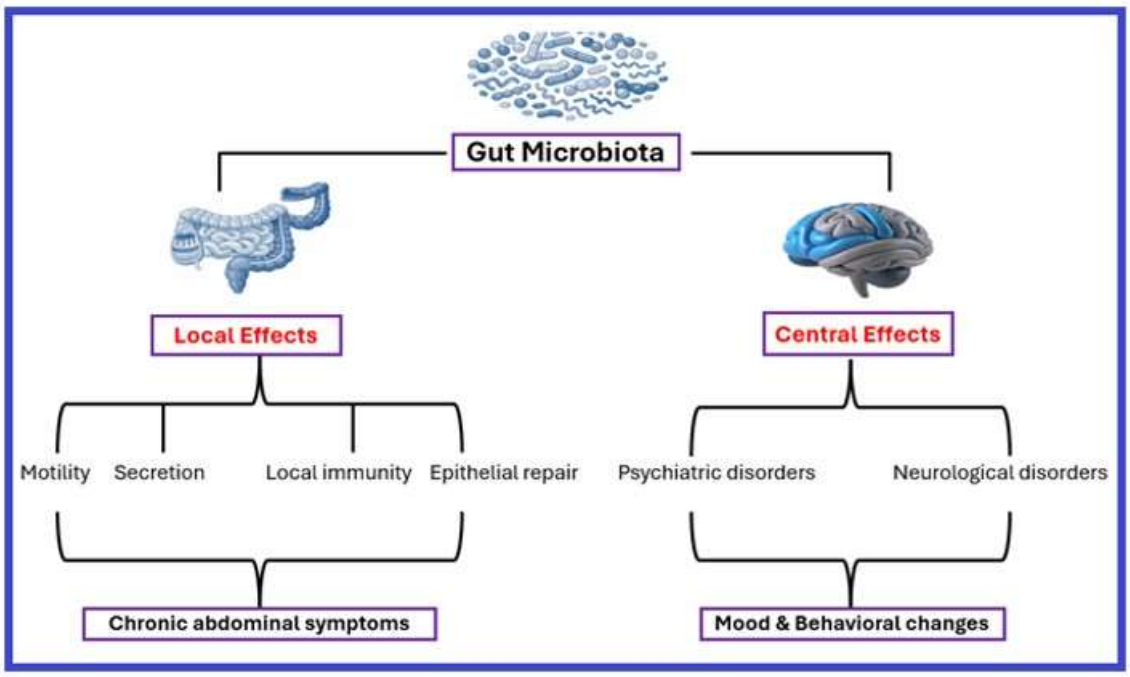


**Figure. 2:** Local and central effects of gut microbiota

The brain possesses the ability to receive and process impulses about the internal physiological homeostatic environment of the viscera, which is called interoception. The unmyelinated autonomic axons are the sole pathway of enteric signals to the

brain. Gut microbiome studies have established that their metabolites represent ~~other~~ major sources of such interoceptive information (Mayer et al., 2006). Rieder et al. (2017) added that the gut microbiota influences the cerebral cortical functions through both direct (nervous) and indirect (vascular) pathways through the gut-brain axis (Figure 3). The gut microbiome is a major integral component that influences the development, structure, and function of the brain, maintaining its health and affecting its disorders' progression through multiple neuroendocrine and neuroimmune mechanisms (Martin et al., 2018; Arifuzzaman et al., 2024).

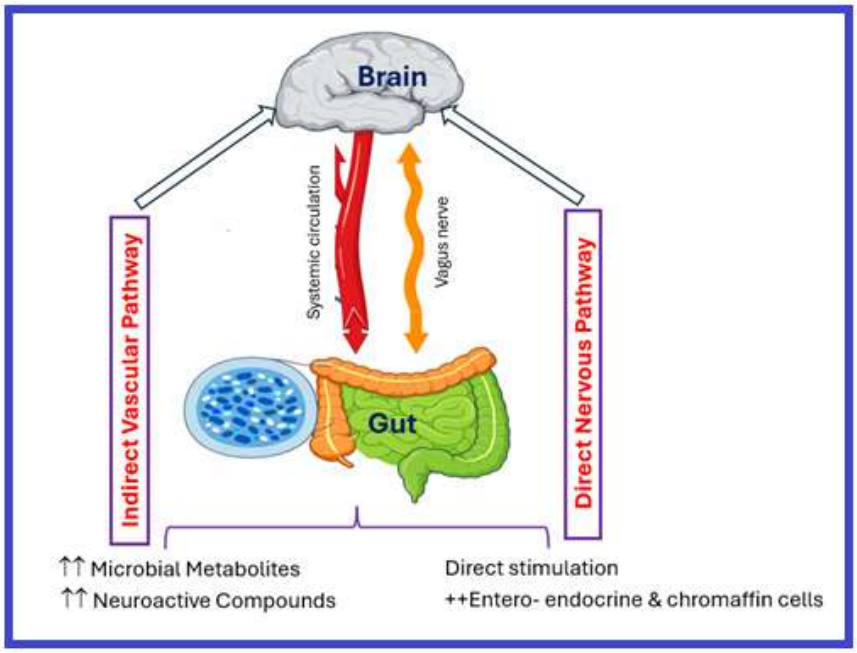


**Figure. 3:** Gut-Brain Axis

A variety of reflex circuits, such as digestive, psychiatric, and neurological states, can affect the homeostasis of the gut-brain axis through the enteric, autonomic, and central nervous regions (Bonaz et al., 2021). The enteric system regulates the physiology of the gastrointestinal secretions, peristalsis, and blood supply during the stable phases. These mechanisms are also controlled by the autonomic nervous system, primarily the vagus nerve, during any hazard to the body's cognitive/emotional health status (Mayer and Tillisch, 2011). The Gut microbiota can produce multiple signals that modulate these reflexes through influencing the local enteric neurons or acting on the afferent vagal neuronal terminals, producing interoceptive signals to the brain. Also, these microbiome metabolites activate receptors of the entero-endocrine and entero-chromaffin gut cells (Walsh and Zemper, 2019). These cells produce different molecules that indirectly stimulate the vagal afferent terminals (Mayer et al., 2022; Jameson et al., 2024).

The indirect (systemic) pathway through which gut microbiota could alter the cerebral functions triggers the release of certain substances in the bloodstream. The stimulation of the local immune system in response to the gut microbes produces pro-inflammatory cytokines, leading to disruption of the activities of the gut microbiome (Cui et al., 2024; Levard et al., 2024). These inflammatory elements affect the endocrine pathway by augmenting the secretion of cortisol and consequent influence on the brain function (Pedraz-Petrozzi et al., 2023). Fukasawa et al. (2025) emphasized that gut bacteria can also influence brain activity indirectly through triggering the release of local neuroactive compounds such as serotonin and GABA, which enter the bloodstream, resulting in modulating the brain response to stress.

The brain responds to these stimulated signals by regulating the vital activities of the sympathetic and parasympathetic autonomic nervous system and by modulating the hypothalamic-pituitary-adrenal pathway. Activation of this pathway enhances the release of adrenocorticotropic hormone and norepinephrine, leading to modifications in the gut microbiome and subsequently gut functions (Kasarello et al., 2023; Tiwari and Paramanik, 2025).

Disturbances in the gut microbiome, interoceptive signals, and neural axes can lead to distress in the whole nervous system. One of the primary interoceptive areas of the cerebral cortex is the insula, mainly its posterior part, while its anterior part incorporates sensory signals with other behavioral or emotional inputs. Other involved cortical areas are the cingulate gyrus and frontotemporal fiber complexes, allowing the integration of interoceptive signals with multiple social and emotional processes (Bonaz et al., 2021). Disorders in these signals are associated with abnormalities in the gut-brain interactions, producing symptoms of various diseases such as dyspepsia, abdominal pain, irritable bowel syndrome, and psychiatric disorders. In addition, they are related to manifestations of some developmental and neurodegenerative diseases (Mayer and Tillisch, 2011; McCallum and Tropini, 2024).

**Barriers to microbiome-gut-brain signaling**

Two main barriers influence the microbiome-gut-brain signaling, which are the intestinal barrier and the blood-brain barrier. These are dynamic barriers, and their permeability is affected by multiple factors, such as stress and inflammation.

**1- Intestinal Barrier**

The intestinal barrier consists of two main layers. The first layer is formed of epithelial cells resting on the lamina propria and interconnected by different types of intercellular junctions like adherens, gap, and tight junctions (Figure 4). These connections maintain the integrity of the epithelial lining, coordinate cellular response, and prevent leakage of the contents of the intestinal lumen, respectively (Sevim et al., 2025).

The second layer is mucus formed of glycans, which are complex sugar molecules with different thickness and structure. This mucus layer is arranged into a lumen-facing loose layer and a deeper layer attached to the epithelial cells. The loose layer is populated principally by commensal organisms for the biofilm generation, and they get nourished by the glycans even in the absence of dietary fibers (Macfarlane and Dillon, 2007). The deep layer is free from bacteria, and it plays a key role in protecting the epithelial tissue from the microbiota. This protection is implemented through the innate immunity, producing antimicrobial peptides, adaptive immunity through the secretion of IgA, and physical separation (Desai et al., 2016). Gut microbiota generates short-chain fatty acids. These fatty acids are essential for preserving the integrity of the intestinal configuration by maintaining the tight cell junctions and decreasing the activation of the immunity of the gut cells (Vaishnava et al., 2008). Diet stress, such as dietary fiber deficiency, or chronic stress, leads to thinning of the mucus layer, increasing the permeability to the microbes. This thinness confronts the cell wall structures of the commensal bacteria with the Toll-like receptors present on the dendritic cells' extensions. These receptors play a key role in communication between the gut microbiome and the immune system homeostasis at the molecular level. They stimulate cytokine release, which produces loosening of the tight junctions between the epithelial cells (Rogier et al., 2015). These alterations allow the gut microbiota to shift through the intestinal barrier, enhancing further activation of the cellular local immunity and propagation across the systemic circulation, which is known as metabolic endotoxemia (Vaishnava et al., 2008). Recent studies concluded that these alterations in the intestinal barrier contribute to various neural disorders (El-Hakim et al., 2022; Pellegrini et al., 2023).

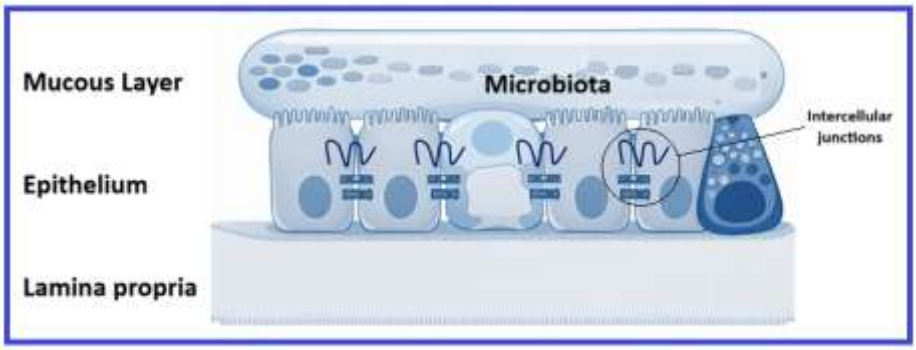


**Figure. 4**: Intestinal Barrier

**2- Blood-Brain Barrier**

The blood-brain barrier regulates the molecular translocation between the cerebrospinal fluid and the circulatory system (Braniste et al., 2014). Increased expression of tight junction factors such as Occludin and Claudin-5 by the gut microbiota

reduces the blood-brain barrier permeability (Alaish et al., 2013). Short-Chain Fatty Acids (SCFAs) produced by the gut microbiota regulate the permeability of the blood-brain barrier, modulate the gene expression of neurons, and influence the immune responses of brain tissues. Other substances produced by the gut microbiota include neurotransmitters, such as dopamine, serotonin, and γ-aminobutyric acid, and SCFAs (Mi et al., 2023), considering that about 90% of serotonin is formed in the gut. Therefore, dysbiosis of the gut microbiota reduces serotonin levels, leading to cognitive and mood disorders (Xiong et al., 2024).

**Modulation of gut microbiome through the autonomic nervous system**

The autonomic nervous system regulates the gastrointestinal motility, secretory function, immune response of the mucosal layer, and ~~the~~ intestinal barrier integrity. Disturbances in this system affect the microbiome habitat, which influences their abundance and diversity (Mayer and Tillisch, 2011). Many pathogenic and commensal gut organisms are vulnerable to dopamine and norepinephrine secreted from the sympathetic postganglionic neurons, causing upregulation of virulence genes and increased interaction and growth of microbes within the gut lumen (Freestone 2013). Intestinal permeability in certain areas of the gut is greatly variable throughout the day. It can regulate the gut lumen microenvironment through alterations in water and nutrient contents. Acute and chronic stress can produce harmful consequences for the intestinal barrier integrity (Deaver et al., 2018). During psychological stress, catecholamines are released by the adrenal glands, causing deterioration of the mucus layer of the intestinal barrier, increasing its permeability and microbiota translocation, which could be compensated by increased expression of tight junction markers after stress exposure (Da Silva et al., 2014; Lauffer et al., 2016).

The reciprocal link between intestinal microbiome and stress represents a major shift in modern neuroscience and immunology that reveals a complex communication network known as the gut-brain-stress axis. Instead of a linear pathway, research showed that stress alters gut microbial composition; in turn, these microbial shifts directly shape how the body regulates physiological stress response [Charitos et al. 2024]. This reciprocal link explains why some individuals experience varying degrees of psychological stress responses. The gut microbiome is an ecosystem that interacts with the nervous, endocrine, and immune systems. Animal and clinical studies showed that gut microbiota function through a well-coordinated network [Lai et al. 2023]. Stress can alter the composition and function of gut microbiota. In contrast, Certain bacteria can influence stress response through multiple signaling mechanisms [Gralczyk-Bikowska et al. 2022].

**Mechanisms of Gut Microbiota-Stress Interaction**

There are three main communicational mechanisms that gut microbiota modulate stress responses through the following mechanisms (Figure 5).

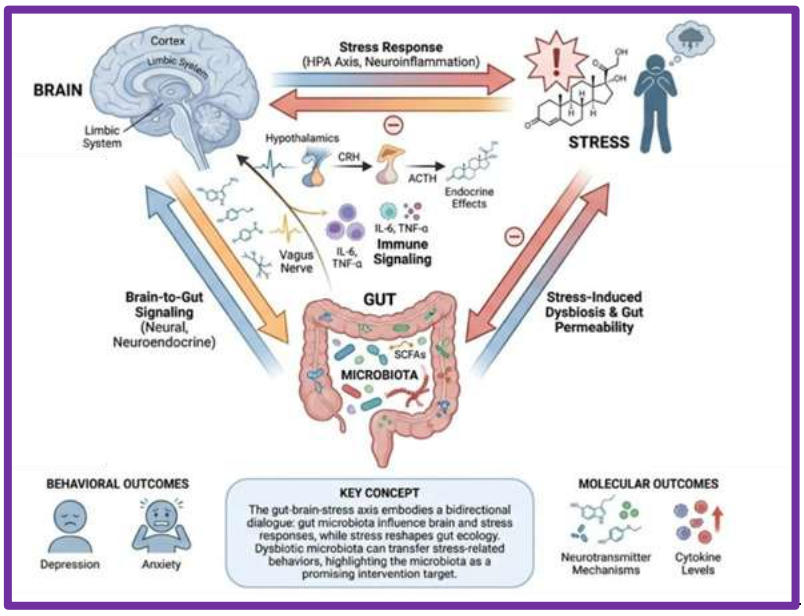


**Figure. 5:** Gut Microbiota-Stress Interaction

### 1- Hypothalamic-pituitary-adrenal (HPA) axis modulation

The hypothalamic-pituitary-adrenal (HPA) axis acts as a primary neuroendocrine pathway regulating the stress response in the human body [Borkent et al. 2022]. The gut microbiota plays a vital role in maintaining HPA axis homeostasis, particularly during stress. The different stressful conditions stimulate the hypothalamus to release corticotropin-releasing hormone (CRH), which stimulates the anterior pituitary to release adrenocorticotropic hormone (ACTH), which ultimately triggers the adrenal glands to produce the cortisol hormone, which is considered the primary stress hormone [Alli et al. 2022]. Under stressful conditions, the blood levels of ACTH and cortisol were significantly elevated compared to those of specific-pathogen-free (SPF) mice. The hyperactive stress response can be reversed by microbial recolonization using the fecal material from control mice at the 9$^{th}$ week of age [Crumeyrolle-Arias et al. 2014, Sudo et al. 2004].

During chronic stress, the gut microbiota modulates the human platelet antigen (HPA) gene expression. Specific bacteria attenuate the expression of the FK506-binding protein 5 (Fkbp5) gene, which is the key regulator of the glucocorticoid receptor's negative feedback loop [Pires et al. 2024]. Absent or disrupted gut microbiota breaks down this feedback loop, the stress response becomes hyperactive, reflecting that gut microbiota directly regulates cortisol level. Thus, depleting gut microbiota using antibiotics will disrupt the glucocorticoid levels. This confirms that gut microbiota plays an active role in controlling the daily circadian rhythm of secretion of the stress hormone that extends beyond acute stress responses [Tofani et al. 2025].

### 2- Microbial Synthesis of Neurotransmitters and Central Mood Modulation

The gut microbiota synthesizes a diverse spectrum of neuroactive compounds that directly affect brain function and emotional states. Specific bacterial strains produce key neurotransmitters and their precursors, including gamma-aminobutyric acid (GABA), acetylcholine, dopamine, serotonin, and norepinephrine, all of which are chemical compounds identical to those found in the nervous system of mammals. These microbial metabolites can reach the brain through multiple routes, which act as signaling molecules [Bear et al. 2020]. An example of such microbial neurotransmitter modulation is demonstrated by the production of gamma-aminobutyric acid (GABA). An experimental study on mice showed elevation of the level of GABA in the cingulate gyrus and its decrease in the hippocampus, amygdala, and locus coeruleus after administration of Lactobacillus rhamnosus for 14 days [Pires et al. 2024]. In addition, the gut microbiota influences the brain through the production of several neuromodulator metabolites. such as SCFAs, particularly butyrate, which is of the most important primary products of bacterial fermentation. Butyrate has been shown to downregulate the Wnt/β-catenin signaling pathway and LRP5 expression, both of which are involved in stress-induced cellular damage [Cui et al. 2025]. Furthermore, metabolomics profiling reveals elevated neuro-related metabolites such as cholate, arachidonic acid, creatine, threosphingosine, erythronic acid, and C18:0 sphingomyelin in probiotic groups compared to the placebo group [Cooke et al. 2022]. In addition, indole, microbial metabolites, help neural signaling pathways by stimulating intestinal enterochromaffin cells (ECCs) to secrete glucagon-like peptide-1 (GLP-1) [Bliss et al. 2018].

### 3- Immune Pathways and Neuroinflammation

The immune system is another pathway through which gut microbiota modulates stress responses and brain function. Gut dysbiosis contributes to increased release of pro-inflammatory cytokines such as interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α). These cytokines can cross the blood-brain barrier (BBB) and activate the HPA axis [Yang et al. 2021, Banks 2005]. The connection between intestinal permeability, immune activation, and stress is particularly well established. Difficult, stressful situations cause a negative effect on the intestinal epithelial barrier, leading to an increase in its permeability [Liu et al. 2023]. This increased permeability allows bacterial lipopolysaccharides (LPS) of the gram-negative bacteria and other microbial-associated molecular patterns (MAMPs) to activate immune responses and trigger HPA axis activation through accumulated cytokines. This demonstrates how gut health can trigger inflammatory responses that form a stressful condition in the brain.

Since the gut microbiota produces immunomodulatory substances such as GABA, acetylcholine, and noradrenaline [Bjurstöm et al. 2008], which creates a reciprocal regulation between neurotransmitter and immune signaling, resulting in activation and maturation of microglial cells, subsequently, these cells will release significant quantities of inducible nitric oxide synthase (iNOS) to modulate nitric oxide (NO) production [Shandilya et al. 2021]. In addition, several species of bacteria have the

capacity to suppress the inflammatory cascade by downregulating toll-like receptor 4 (TLR4) and NF-κB signaling pathways [Shao et al. 2021].

**Experimental rodent models: understanding the mechanisms of gut-brain axis**

**Germ-Free (GF) and Microbiota Depleted Rodent Models**

Researchers found that GF mice have lower anxiety-like behavior and differences in brain neurochemistry compared to SPF mice [Crumeyrolle-Arias et al. 2014, Sudo et al. 2004]. Eliminating gut microbiota in wild-type mice using broad-spectrum antibiotics produced similar results in other studies [Bliss et al. 2018]. These findings show that even a short disruption of gut microbiota is enough to affect the stress response. Despite the importance of which antibiotics are used, and for how long, the timing of microbiota modeling significantly outweighs these factors in determining the precocious maturation of the hypothalamic-pituitary-adrenal axis with a gender specific response [Neufeld et al. 2011]. Notably, when under stressful conditions, the Griseofulvin mouse model exhibits elevated corticosterone and adrenocorticotropic hormone levels that are partially reversible by fecal microbial transplant or single Bifidobacterium infantis administration, demonstrating the therapeutic potential of specific bacterial recolonization [Shropshire et al. 2016 Desbonnet].

**Interventions and Stress Attenuation**

A large amount of preclinical evidence indicates that supplementation with specific bacterial strains can attenuate induced behavioral changes and stress responses. Clinical and experimental studies have revealed that the inhibition of stress-induced HPA axis hyperactivity, as well as the mitigation of depressive like behavior and anxiety-related behavior, is mediated in part by targeted probiotics containing Bacillus licheniformis, Saccharomyces boulardii, Lactobacillus rhamnosus, and Bifidobacterium spp [Desbonnet et al. 2010; Eutamene et al. 2007]. Among the most thoroughly investigated strains, Lactobacillus plantarum PS128 has been shown to reverse dysbiosis-induced depressive phenotypes when administered to GF mice, with its therapeutic effects mediated via both neurotransmitter signaling and immunomodulation Alli et al 2022, Liu et al. 2016].

Furthermore, particular Lactobacillus and Bifidobacterium species demonstrate a distinct, species-specific efficacy regarding their stress-reducing properties. For instance, single-strain monocolonization of Bifidobacterium subtilis in GF mice significantly attenuates restraint-induced elevation in plasma Corticosterone and ACTH levels [Sudo et al. 2004]. Similarly, Bifidobacterium adolescentis NK98, B. adolescentis IM38, and B. longum NK46 suppress corticosterone surge under acute stress conditions [Han et al. 2019; Jang et al. 2018; Jang et al. 2019]. In contrast, B. Pseudocatenulatum CECT 7765 [Moya-Pérez et al. 2017] and B. bifidum G9-1 (BBG9-1) [Fukui et al. 2018] preferentially alleviate maternal separation-induced stress responses. Remarkably, the widely cited psychobiotic strain L. rhamnosus JB-1 has been shown to increase GABA expression and decrease anxiety-like behaviors in a vagus-nerve- dependent manner in rodents. However, clinical elevation in humans revealed that this same strain failed to alter cortisol profile or mitigate perceived stress, the often observed gap between preclinical efficacy and clinical translation [Kelly et al. 2017].

**Early Life Stress and Critical Developmental Windows**

Previous studies investigated the specific microbial alteration induced by early life stress. Maternal separation is one of the early life stressors. These early life stressors disrupt the normal development of gut bacteria, leading to higher stress sensitivity and lower levels of Lactobacillus in adult mice [Bailey et al. 1999]. Prenatal stress leads to depressive-like behavior in adult mice. By altering the gut microbiota composition that is associated with HPA axis response to stress [Lach et al. 2018]. Moreover, prenatal stress induces a significant decrease in the abundance of beneficial bacteria such as Bifidobacteriaceae, Rikenellaceae, and S24-7, along with an increase in pro-inflammatory proteobacteria [Gubert et al. 2020]. In contrast, administration of L. reuteri alleviates anxiety-like behaviors via oxytocinergic and dopaminergic signaling [Zhu et al. 2024].

**Human Studies: Clinical Findings and Their Therapeutic Implications**

**Relations of chronic stress and the microbiota-gut-brain axis in adolescents**

One in seven (14.3%) of adolescents live with mental health problems worldwide, which remain largely untreated (WHO, 2025). Chronic stress has appeared as a main risk factor for mental health diseases in adolescents (Licinio and Wong, 2023). Early life stress and psychological childhood trauma during critical periods of maturation and development increase the risk of long-term psychological conditions (Lowry et al., 2022; Shin and Kim, 2023). Adolescence is a critical developmental phase. It is a highly

sensitive period for brain growth and neuroplasticity. The gut microbiome has been shown to play a crucial role in this progression. They generate metabolites and compounds important for brain and mental health (Fuhrmann et al., 2015). Recent studies on the etiology and pathogenesis of mental disorders continue to reveal the complex, multifactorial relationships between gut and brain (gut-brain axis). This relationship includes immune, endocrine, inflammatory, and nervous mechanisms (Warren et a., 2024; Ying et al., 2025). Many psychiatric pharmacotherapy interventions produce antimicrobial effects, altering the gut and neural environment (Rea et al., 2020). Therefore, there is a need for efficient prevention and treatment approaches for the primary illness, its risk factors, and the wide range of comorbidities associated with it.

Current evidence of alterations in gut microbiota composition due to chronic stress originates principally from animal and adult human studies. However, records from adolescents remain insufficient. Michels et al. (2019) reported that adolescents experiencing high stress had a lower alpha diversity. This confirms the theory of the gut-brain axis. High stress, especially in adolescents, due to continuous school pressure, examination stress, social anxiety, and family engagement, activates the brain to produce stress hormones and neurotransmitters. These substances directly influence the gut microbiota. They affect gut peristalsis, increase intestinal leakage by altering its permeability, and modify the secretions that nourish gut bacteria. This cascade creates a hostile environment for beneficial microbiota, allowing the stress-resistant species to dominate and thereby decreasing diversity. Moreover, by reducing microbiome diversity, the formation of essential metabolites such as short-chain fatty acids (SCFAs) is affected. These metabolites regulate inflammation and mood, significantly in adolescents, and their reduction potentially increases depression and anxiety, leading to further stress and negative feedback, producing more vicious cycles (Dinan and Cryan, 2017; Sherwin et al., 2019).

**Microbiota and the sensitive periods of brain development**

How the gut microbiota grows over the life span is studied by recent sequencing technologies. At birth, the microbiota is rapidly propagated. Most of the early gut colonists are transmitted from the mother to the vaginally delivered fetuses through the maternal vaginal or fecal microbiota (Ferretti et al., 2018). In the first few days, the primary function of the early microbiota is to extract nutrients, supporting the rapid development of the brain and the rest of the body (Hollister et al., 2015; Timmerman et al., 2017). One of the multiple benefits of breastfeeding is the supply of a combination of nutrients that plays a fundamental role in the regulation of the immune system and the enhancement of the growth and function of useful microorganisms (O'Sullivan et al., 2015; Milani et al., 2017). The following rapid burst in the composition of microbiota is at weaning with the spike of inflammatory activation termed "weaning reaction". Microbiota development is crucial at weaning for the maturation of the immune system, which is one of the elements of gut-immune-brain pathways. Disruptions of weaning reaction led to pathological establishment of the immune system with the risk of inflammatory disorders and subsequent immune diseases (Al Nabhani et al., 2019; Guevarra et al., 2018). Then, weaning is followed by an ongoing change and plasticity through middle childhood into adolescence (Derrien et al., 2019).

During the sensitive periods, also known as critical windows or critical periods, the systems reveal heightened plasticity, which responds to environmental cues and expected inputs, allowing them to function in an ideal and effective manner. Several sensitive periods are expected to occur through the development of the microbiota-gut-brain axis, matching those happening within each area of neurodevelopment. Examples of these sensitive periods include the development of complex higher-order brain functions such as language, emotional learning, and behaviors (Alberini & Travaglia, 2017; Tottenham, 2017). Signals from the gut microbiota act as an expected input to regulate the gut-brain axis. Absence of this axis during any specific developmental period produces an inconsistent effect on certain functions relevant to the time window of interruption and could interfere with the system control as a whole (Cowan et al., 2020). Previous studies observed sex-specific complex relationships between the gut microbiota composition and the very early nature, biological behavior, and emotional patterns of the host, including the specific personality trait and fear reactivity (Aatsinki et al., 2019). Disruption of the microbiota, due to any gastrointestinal distress, has been found to anticipate future anxiety during childhood (Callaghan et al., 2020). Cowan et al. (2020) mentioned that modulation of gut microbiota enhances the behavioral symptoms of neurodevelopmental disorders in pediatrics. Other studies investigated the association between microbiota and cognitive performance. At one year of age, stool microbiota can predict cognitive performance on the global cognitive index: The Early Learning Composite, of the Mullen scale at 2 years. This outcome was determined by the differences in the receptive and expressive language domains (Carlson et al., 2018; Gao et al., 2019).

It has been documented that the use of antibiotics in the first year of life harms the general IQ and reading abilities in the child, affecting their primary school performance (Slykerman et al., 2017). These antibiotics reduce the diversity and composition of the gut microbiota (Yassour et al., 2016). These changes affect the children's health, increasing vulnerability to a variety of microbial pathogens and multiple mental health problems (Arrieta et al., 2014). These findings confirm that early antibiotic exposure influences the relationship between microbiota and the cognition, emotions, and attitude of the children and could lead to major behavioral consequences, depression, and symptoms of ADHD. In addition, perinatal antibiotic administration to the mother during pregnancy or the neonate significantly produced attentional problems before the age of five years. Moreover, the children exposed to antibiotics were found to reveal increased delta power on EEG, which is observed in ADHD, and exhibited a delay in maturation and development (Firestein et al., 2019). Another research investigated the transplantation of fecal microbiota of preterm neonates with poor-growth microbiota into mice. They showed delayed brain development with a deficiency of neuronal differentiation markers, delayed myelination of cerebral cortex white matter, reduced oligodendrocyte development, high levels of neuroinflammation, disruption of multiple neurotransmitter circuits, and low levels of growth hormones (Lu et al., 2018).

Chronic stress in adolescents was associated with increased richness of Rhodococcus, Bacteroides, Parabacteroides, Roseburia, and Methanobrevibacter, but reduced Phascolarctobacterium at the group level (Michels et al. 2019). In addition, chronic stress affects the levels of gut Anaerostipes and Parabacteroides in adolescents with inflammatory bowel disease (Mackner et al., 2020). Ying et al. (2025) detected that the composition of gut microbiota exhibited reduced alpha diversity and altered beta diversity in the high-stress adolescents' group. The authors recognized five reduced genera: Faecalibacterium, Bacteroides, Akkermansia, Lachnospiraceae unclassified, and Ruminococcus in adolescents suffering high-chronic stress. Furthermore, their study discovered high levels of other species: Streptococcus suis, Ruminococcus sp. CAG 108, Bifidobacterium catenulatum, and Phascolarctobacterium faecium in the chronic stress group, with 19 differential metabolites related to one or more of these altered species in the metabolomics profiling. Other studies on adolescents observed that high inflammation levels detected due to chronic stress are associated with decreased levels of Faecalibacterium, Akkermansia, and Lachnospiraceae (Davis and Latimer, 2023; Li et al., 2023; Hajjo et al., 2023). Faecalibacterium generates SCFAs in the cecum and diminishes the release of inflammatory cytokines under chronic stress (Li et al., 2022; Mohebali et al., 2023). Akkermansia is considered a next-generation probiotic. It can regulate intestinal inflammation and metabolic dysfunction (Cani et al., 2022; Guo et al., 2024). Lachnospiraceae accelerate the degradation of dietery fiber and formation of SCFAs in addition to its anti-inflammatory benefits (Hoffmann et a., 2016).

**Observational and Correlational Studies**

Modern clinical research into the gut-microbiota-brain axis has advanced significantly, with numerous large-scale studies establishing a strong correlation between specific microbial alteration and stress-related psychiatric symptoms. For example, in the Flemish gut flora project involving 1,054 subjects, fecal Dialister and coprococcus spp. were found significantly to be reduced in depressed individuals even after accounting for any interfering effects of antidepressant therapy [Valles-Colomer et al. 2019]. Similarly, a Swiss cohort study demonstrated that higher stress, depression, and anxiety symptoms were associated with inflammatory bowel disorder (IBD) during clinical convalescence [Järbrink-Sehgal et al. 2020].

Previous studies in patients with depression found a reduction in overall gut microbiota diversity, richness, and taxonomic composition, and an alteration in the prevalence of the phyla Bacillota, Bacteroidota, and Actinomycota [Charitos et al. 2024]. This taxonomic shift is linked to specific metabolic alterations. For example, in depressed individuals, profiling of SCFA showed an increase in isocaproic acid and a decrease in propionic acid compared to healthy individuals [Gralczyk-Bikowska et al. 2022]. According to Karolinae et al., positive self-judgment was correlated with high levels of Lactobacillus species in stool samples, while indirectly correlated with lower depression scores [Skonieczna-Żydecka et al. 2018].

**Prenatal Stress and Its Impact on Neonatal Microbiota**

Maternal stress affects offspring microbiota and stress susceptibility. Women reporting a high level of psychological stress and elevated salivary cortisol levels during pregnancy delivered newborns with a higher abundance of Proteobacteria, alongside lower relative abundances of lactic acid bacteria such as Lactobacillus, Lactococcus, Aerococcus, and Bifidobacteria [Zijlmans et al. 2015].

**Probiotic Intervention in Clinical Trials**

Probiotic intervention with Bifidobacterium longum showed various outcomes [Bear et al. 2020]. Bifidobacterium longum 35624 supplementation ($1\times10^9$ CFU/day) was observed over a period of off-season training in university-level female athletes and resulted in decreased serum IL-1ra and salivary IgA levels at mid-training in comparison to the placebo group, which indicates that the intervention's efficacy may depend on the population studied and the timing of administration [Cooke et al. 2022]. These distinct physiological outcomes underline a critical paradigm in human microbiome studies: this may indicate that the intervention's efficacy may be dependent on the population studied and the timing of administration, the relation between microbiota and stress may depend on host genotype, sex, and developmental state, and there might be critical windows of development during which the gut microbiota have more effect [Bear et al. 2020].

**Acute versus chronic stress effects on microbiota and stress**

**Acute stress (short-term stress) effects**

Acute stress, also known as short-term stress, results in measurable, but usually transient, alterations in microbiota function and composition. Various processes appear to occur simultaneously to produce these effects, with the specific mechanisms of these effects differing significantly even to the species level [Bear et al. 2020]. Acute stress can alter HPA axis activation, changes in intestinal motility and permeability, and tryptophan/kynurenine metabolism, often without the sustained inflammatory phenotype observed in chronic stress [Bear et al. 2020].

Multiple studies have demonstrated that inhibiting vagus nerve signals does not diminish the behavioral changes induced by microbial dysbiosis; however, the vagus nerve frequently mediates acute stress effects on the microbiota, suggesting redundancy and stress-related neural pathways [Bear et al. 2020].

**Chronic Stress or Long-Term Stress and Dysbiosis**

Chronic stress, also known as long-term stress, can result in profound, lasting changes in microbiota composition. Chronic stress leads to alterations in gut microbial composition, especially increased levels of Clostridium and decreased Bacteroides [Pires et al. 2024]. Multiple studies showed a significantly low level of Lactobacillus under chronic stress conditions. Chronic stress alters the tryptophan kynurenine metabolic pathway and disturbs neuroendocrine homeostasis via the gut-brain axis, and facilitates the development of depression-like behavior [Cui] et al. 2025. Furthermore, persistent stress signaling is transmitted to the brain via the vagus nerve as well as afferent/efferent neuron circuits, establishing a chronic feedback loop that sustains both mood disturbances and microbiota dysbiosis [Wang et al. 2024]. The strong evidence of this causative relation is fecal microbiota transplantation (FMT). Transplanting fecal microbiota from depressed donor mice leads to depression in healthy recipient mice. This indicates that the dysbiotic microbiota itself carries the ability to induce mood disorders in naive mice [Thabet et al. 2024]. This provides a very important concept that microbiota dysbiosis is not a sign of depression, but also plays a causative role.

**Conflicts of Interest**

The authors declare no conflict of interest.

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