Chinese Journal of Laboratory Medicine

Microbial Influences on Adolescent Emotions: Navigating the Gut-Brain Axis in Mood Disorders

Dr Srinidhi Rai [1], Janice DSA [2]

[1]Additional Professor, Department of Biochemistry, K S Hegde Medical Academy, Nitte (Deemed to be University) Mangalore, Karnataka

[2]Associate Professor, A J Institute of Medical Sciences and Research Centre, Mangaluru, Karnataka, India

DOI: https://doie.org/10.0709/Cjlm.2024274358

Abstract:
The gut-brain axis has garnered increasing attention for its role in shaping emotional well-being, particularly during adolescence, a critical period marked by significant physiological and psychological changes. This paper explores the complex interplay between microbial influences and adolescent emotions. Through a comprehensive review of existing literature, we examine the bidirectional communication pathways linking the gut microbiota to emotional states and mood regulation. Evidence suggests that alterations in gut microbial composition may contribute to the pathophysiology of mood disorders in adolescents, influencing neurotransmitter synthesis, immune function, and stress response pathways. Furthermore, dietary habits emerge as a key modulator of the gut microbiome, with implications for emotional health. Strategies targeting dietary modifications and microbial balance hold promise in promoting positive emotional outcomes among adolescents. Interdisciplinary collaborations among researchers, clinicians, and educators are essential to advance our understanding of the gut-brain axis and develop tailored interventions to support adolescent mental health. This abstract underscore the importance of elucidating microbial influences on adolescent emotions and navigating the intricate dynamics of the gut-brain axis in mood disorders.

Key words: Gut Microbiota, Adolescent period, Gut Brain Axis

Introduction:

Adolescence is a stage of life with unique requirements and rights in terms of growth and health. It's also a time to gain information and talents, practice managing relationships and emotions, and develop qualities and skills that will be necessary for living a happy adolescent life and fulfilling adult roles. Children are particularly vulnerable during this period because they may encounter many adolescent issues, such as improper behaviors, that could cause serious issues down the road. This is an exciting and intimidating moment for anyone going through changes in their lives on a biological, cognitive, psychological, social, moral, and spiritual level. Greater independence leads to greater freedom, but greater freedom also entails greater responsibility. Close family members frequently feel as though they are suddenly living with a stranger as attitudes and viewpoints shift. It can be challenging for parents to connect with their children during this time due to concerns about adolescent behaviour.

Encouraging teenagers to recognize and differentiate between depressive and healthy thought processes is a wonderful first step. Assisting parents and friends in creating a solid support

network for the teenager is also crucial. The main psychological risk factor for suicide, the second-leading cause of mortality for teenagers, is depression. During adolescence, the prevalence of depressive illnesses rises significantly (1). Studies have shown that the post pubertal period is associated with an increase in depressive disorders in India (2) Although a wide range of biological, psychological, and social factors contribute to mood disorders. there is a growing body of research focusing on the need to comprehend any potential molecular mechanisms behind them. Nonetheless, there is evidence that the gastrointestinal tract's microbes and the genetic material they carry may have a significant impact on mental health. (3). The possibility that gut microbiota plays a role in teen mood problems has drawn more attention in the past few years. This review delves into the latest research on the gut-brain axis and its connection to mood disorders in teenagers, offering insights into possible pathways and clinical applications. Deciphering how microbial populations affect teenage emotions could be very helpful in diagnosing, treating, and avoiding mood disorders.

Dynamics of the Adolescent Period Gut Microbiota

Advances in next-generation microbial sequencing technology have made it possible to uncover trends in diversity across the life span and to more accurately analyse the individual bacteria that make up the human gut. (4). Study examined the differences in the distal intestine microbiota composition between adults and adolescents (aged 11–18). There was a statistically significant increase in Bifidobacterium and Clostridium bacteria in adolescents. (5). A study by Yuan X et al. analysed the biodiversity of gut microbiota at different pubertal stages. Firmicutes, Bacteroidetes and Proteobacteria were the dominant phylum in both pubertal and non-pubertal stages. There was no variation in alpha- and beta-diversity between the various phases of puberty. Members of the family Clostridiaceae, genus Coprobacillus, and order Clostridiales were substantially more common in non-pubertal subjects than in puberty subjects. Additionally, compared to the non-pubertal subjects, the pubertal subjects had a significantly higher prevalence of members of the class Betaproteobacteria, order Burkholderiales. (6). A varied colony of bacteria reside in the gut, and they change throughout life in response to environmental and physiological stimuli. It's interesting to note that a significant number, if not all, of the stressors encountered by teenagers have been shown to have an impact on the intestinal lumen's bacterial composition. Alterations to the gut microbiota are caused by antibiotic use, alcohol and drug use, stress, nutrition, and alterations in sleep patterns. (7-11). We are left with pertinent questions regarding the potential role of these bacteria in the psychiatric disorders that frequently emerge during the adolescent years, given that adolescents are exposed to such a wide range of external challenges and stressors, all of which have known effects on the intestinal microbiota.

Exploring the Link: Adolescent Dietary Patterns and Gut Microbiota Composition

“Let food be thy medicine and medicine be thy food.” ― Hippocrates. Hippocrates' famous proverb, which dates back more than 2,000 years, may still apply today given the increased awareness of the role nutrition plays in preserving overall health, including mental health.

Adolescence is a developmental stage in which children become more independent of their parents in a variety of cognitive, social, and behavioural domains, including the acquisition, preparation, and consumption of food. (12,13) Obesity is increasing at an alarming rate in adolescents. A Mediterranean diet is abundant in fruits, vegetables, whole grains, legumes, and

nuts, while a Western diet is heavy in dairy products, animal proteins, and fats. Western diet increased the chances of obesity, alterations in the diet could reverse western diet induced obesity, suggesting that dietary changes can influence the impact of gut microbiota on host metabolism (14). Shankar et. al. study, which contrasted US teens fed a Western diet with Egyptian teenagers exposed to a Mediterranean diet, demonstrated how nutrition affects the makeup and functionality of the adolescent gut microbiota. While the Mediterranean diet enriched microorganisms engaged in polysaccharide breakdown, the Western diet enriched microorganisms that broke down proteins and carbohydrates. (15)

Gut Microbiota-Brain Communication: - Exploration of the pathways through which gut microbiota influence brain function.

The gut microbiota has an impact on the physiological, behavioural, and cognitive functions of the brain, even though the exact mechanism remains not fully comprehended. The gut microbiota-brain axis is considered to be bi-directional. (16) The bidirectional communication between the gut and the brain underscores the dynamic relationship between these two systems.

There is evidence indicating the existence of five communication pathways between the gut microbiota and the brain. These pathways encompass the neural pathway, the neuroendocrine-hypothalamic-pituitary-adrenal axis, the gut's immune system, neurotransmitters, and neural regulators produced by gut bacteria, as well as barrier pathways like the intestinal mucosal barrier and the blood-brain barrier (BBB). (17)

1.**The neural pathway**

The neurological pathway comprises the vagus nerve (VN), the autonomic nervous system (ANS), the enteric nervous system (ENS), and the modulation of neurotransmitters within the gastrointestinal tract. (17,18)

The gut and the brain communicate through two pathways. Firstly, there's a direct exchange of information between the gut and the brain via ANS and the VN in the spinal cord. The second pathway involves bidirectional communication between the ENS and the ANS and VN within the spinal cord. The control of gut functions follows a four-level organization, namely, ENS, prevertebral ganglia, ANS in the spinal cord and brain stem, and higher brain centers. (19,20)

Direct neural communication between gut microbiota and the brain occurs mainly through the VN. The VN spans from the brain to the abdomen and plays a crucial role in overseeing the functions of internal organs, including digestion, heart rate, and respiratory rate. Consisting of both efferent and afferent neurons, the VN facilitates the transmission of motor signals between the brain and intestinal cells, which are additionally influenced by the gut microbiota. (16)

The afferent branch of the VN is the primary neural connection between the GI tract and the brain. The afferent fibers do not interact with the gut microbiota directly. However, microbial metabolites or microbiota-mediated modulation of enteroendocrine and enterochromaffin cells (ECCs) in the gut epithelium can influence the VN. (21)

Experiments involving vagotomy in mice underscore potential connections between the VN and communication between the central nervous system and microbiota. These findings may

have implications for mood and neurobehavioral disorders in humans. Specifically, vagotomy in mice has been demonstrated to impede the central signalling of Lactobacillus and Bifidobacterium species, leading to the inhibition of their mood-modifying effects. (22)

The ECCs in the GI tract also play a crucial role in the bidirectional communication. These cells are responsible for synthesizing and releasing serotonin (5-HT), a neurotransmitter that contributes significantly to mood regulation and overall well-being. Additionally, enterochromaffin cells respond to various microbial stimuli, including short-chain fatty acids (SCFAs) and secondary bile acids (2BA) produced by gut bacteria, such as clostridials. (23)

These microorganisms enhance their stimulatory effects on ECCs when there is an elevated availability of dietary tryptophan. Furthermore, ECCs establish communication with afferent nerve fibers through synaptic connections formed by neuropod-like extensions of ECCs. Conversely, the ANS has the capacity to activate ECCs, leading to the release of 5-HT into the gut lumen. In this environment, serotonin can be absorbed through serotonin transporter-like mechanisms, influencing the functionality of gut microbes. (24)

2. The neuroendocrine-hypothalamic-pituitary-adrenal axis

Gut microbiota plays a crucial role in the development of the neuroendocrine system. There is evidence to show that the gut microbiota regulates the response of hypothalamus-pituitary-adrenal (HPA) axis to stress. (25-27)

Sudo and colleagues (2004) and Clarke and colleagues (2013) demonstrated exaggerated response of the HPA axis in separate studies carried out on germ free (GF) mice. (25, 26) GF mice have been instrumental in understanding the intricate relationship between the host and gut microorganisms.

Furthermore, Vagnerova K et al (2019) showed that the gut microbiota exerts a significant modulating influence not just on brain neurochemistry but also on the pituitary and adrenal glands, as well as extra-adrenal tissues. (27) They found that lower expression of Pomc (pro-opiomelanocortin) and Crhr1 (corticotropin-releasing hormone receptor 1) in the pituitary of Specific Pathogen-Free (SPF) mice could partly account for the heightened HPA axis response in GF mice. Pomc is a precursor protein that gives rise to various biologically active peptides. These include adrenocorticotropic hormone (ACTH), which plays a role in the regulation of the adrenal glands, and beta-endorphins, which are involved in pain regulation and mood. (28) On the other hand, Crhr1 is a receptor for corticotropin-releasing hormone (CRH), a peptide involved in the regulation of the stress response and the HPA axis. Activation of Crhr1 is part of the signaling pathway that leads to the release of ACTH and, subsequently, cortisol from the adrenal glands in response to stress. (29)

Stress and the HPA axis, in turn, can impact the composition of the gut microbiome. Early stress and maternal separation result in long-term changes in both the HPA axis and the microbiome. (30,31) Stress-induced alterations in the gut microbiome include changes in the abundance of specific bacteria, such as Bacteroides and Clostridium, and increased levels of inflammatory markers like interleukin-6 (IL-6) and monocyte chemotactic protein 1 (MCP-1). These findings highlight the intricate interplay between stress, the HPA axis, inflammation and the gut microbiota. (32)

3. Gut's immune system

The interplay between the immune system and gut-brain signalling cannot be overlooked. Cerebrovascular accidents, Alzheimer's disease, Parkinson's disease, epilepsy and several other neurological conditions involve low-grade systemic inflammation. This inflammation signals a malfunctioning immune response and dysbiotic microbiota. (33)

The mucosal immune system in the GI tract, composed of lamina propria and gut-associated lymphoid structures, provides protection against microbial attacks. (33) The immune response to microbes is facilitated by toll-like receptors (TLRs) and peptidoglycans (PGNs), which function as detectors. (34) When the microbe penetrates deep into the mucosal layer of the GI tract, it is taken by specialized antigen presenting cells (APCs), known as dendritic cells (DCs). The DCs present the microbial antigens to T- and B-lymphocytes in the mesenteric lymph nodes. (35)

The penetration of microbes into the mucosal barrier of the GI tract is prevented due to a robust physical barrier and presence of immunoglobulin A (IgA) and antimicrobial peptides in the GI lumen. (33)

During eubiosis, DCs present antigens to lymphocytes in the gut-associated lymphoid tissue (GALT), leading to the generation of T-regulatory cells (Tregs). Tregs subsequently produce anti-inflammatory cytokines, such as IL-10 and TGF-β. These cytokines play a pivotal role in suppressing the production of proinflammatory cytokines, causing a shift in the immune response from Th1/Th17-dependent to Th2-dependent. This shift dampens the immune reaction and supports the repair process in damaged tissue. Moreover, induced Tregs may circulate and inhibit inflammatory responses throughout the organism. (36)

During dysbiosis, an initial local inflammatory response occurs in the gut, followed by the development of peripheral inflammation when inflammatory mediators, bacteria, metabolites, Pathogen-Associated Molecular Patterns (PAMPs), etc., enter the systemic circulation. Both innate and adaptive immune mechanisms are activated, with PAMPs activating innate immunity through Pattern Recognition Receptor (PRR) receptors on host cells. In GALT, immune cells are activated during dysbiosis, and lymphocytes differentiate into proinflammatory subtypes (Th1 and Th17) under the influence of inflammatory mediators and PAMPs. This results in the production of proinflammatory cytokines, such as interleukin-2 (IL-2), interleukin-12 (IL-12), TNFα, IFN-γ, and Th-17. Peripheral inflammation compromises BBB integrity, enabling the infiltration of immune cells and inflammatory mediators into the CNS. Bacterial toxins circulating in the bloodstream may also infiltrate the CNS. Microglia, the resident immune cells in the CNS, can be activated by infiltrating proinflammatory cytokines, triggering a sterile immune reaction and potentially causing injury to the CNS. (33,36)

Compelling support for the link between the immune system and the gut-brain axis emerged when mice raised in a germ-free (GF) environment displayed underdeveloped GALT, decreased counts of intestinal lymphocytes, reduced production of immunoglobulin (Ig) A, and compromised levels of antimicrobial peptides. While many of these deficiencies can be rectified through microbiota colonization, some components can only be fully restored if colonization takes place early in the developmental stages. (37)

4. Neurotransmitters and neural regulators produced by gut microbiota

The microbiota in the gut has the capability to produce various compounds including gamma amino butyric acid (GABA), 5-HT, dopamine, and short-chain fatty acids (SCFAs).

GABA is a non-protein amino acid and a major inhibitory neurotransmitter. (38) Low levels of GABA are linked with generalized anxiety, depression, autism, schizophrenia and epilepsy. (39) Certain strains of Bifidobacterium and Lactobacillus bacteria exhibit the fascinating ability to produce GABA. (16) The potential impact of these GABA-secreting bacteria on the gut-brain axis is an area of growing interest in research.

Serotonin, also known as 5-hydroxytryptamine (5-HT), is a neurotransmitter that plays a crucial role in various physiological functions within the central nervous system (CNS) and the gastrointestinal (GI) tract. In the CNS, 5-HT is involved in regulating mood, appetite, sleep, and cognitive functions. (1) Imbalances in 5-HT levels have been associated with various conditions, including neuropsychiatric disorders, as well as gastrointestinal disorders like irritable bowel syndrome (IBS). (40,41) As described earlier, 5-HT is synthesized and released by enterochromaffin cells, under the influence of microbial influence. The resident microbiota in the gut plays a role in regulating both tryptophan and serotonin, directly and indirectly. Indirectly, the gut microbiota influences tryptophan availability and 5-HT formation through the kynurenine pathway. (42) Recent findings from germ-free animals without gut microbiota reveal that they have elevated circulating tryptophan and reduced serotonin levels. (26, 43) Introducing tryptophan-metabolizing bacteria to their gut lowers circulating tryptophan, affecting hippocampal 5-HT concentrations in male germ-free animals. (26)

Dopamine, another potent neurotransmitter, is a precursor of catecholamines like epinephrine and norepinephrine. Decrease in dopamine levels is associated with motor deficits as seen in Parkinson's disease, schizophrenia and addiction. (16) Certain microbial species have been identified as potential modulators of receptors, transporters, and specific targets within the dopaminergic pathway. This modulation can occur in either a positive or negative manner, indicating a nuanced relationship between these microbes and dopamine-related processes. (44) Despite these compelling findings, the underlying mechanisms governing how these microbes influence the dopaminergic system remain incompletely understood. Further investigation is necessary to unravel the specific pathways and molecular processes through which these microbes impact dopamine regulation, shedding light on potential therapeutic avenues for conditions involving dopaminergic dysregulation.

SCFAs are organic monocarboxylic acids such as acetate, propionate and butyrate. They are characterized by a chain length of up to six carbon atoms. They serve as the primary outcomes of anaerobic fermentation, specifically from indigestible polysaccharides like dietary fiber and resistant starch, a process carried out by the microbiota located in the large intestines. (45) SCFAs are known to regulate the gut health by maintaining the integrity of the intestinal barrier, production of mucus and immune response following inflammation. (46) They can also influence neurotransmitters such as glutamate, glutamine, GABA and others. (47) SCFAs such as propionate and butyrate can trigger the cell signaling pathway through changes in intracellular potassium concentration and regulate the gene expressions of the enzymes tryptophan hydroxylase and tyrosine hydroxylase. Tryptophan hydroxylase is required for the synthesis of 5-HT while tyrosine hydroxylase is required for the synthesis of dopamine,

adrenaline and noradrenaline. (48,49) Their role is not limited to the intestines, but also extend into systemic circulation and cross the blood brain barrier (BBB) with the help of specific transporters. (50) SCFAs are found in relatively low concentration in the brain under normal physiological conditions. (51) There is evidence to prove that SCFAs can influence the BBB. In a study carried out by Braniste V et al, adult GF mice that were allowed to colonize with SCFAs producing bacterial strains showed a restoration of BBB integrity. (52) Furthermore, oral administration of three main SCFAs, namely, acetate, propionate and butyrate, in GF mice showed alleviation in the maturation process of microglia. (53)

Another neural regulator to be noted is brain-derived neurotrophic factor (BDNF). BDNF plays a major role in supporting the development of neurons and synapses that regulate emotions and cognition. (54) BDNF is formed from the cleavage of prepro-BDNF into pro-BDNF which eventually forms mature BDNF. (55) The proteolytic system responsible for this cleavage, specifically the tpa/plasminogen system, becomes involved in the development of depression. (56) The levels of BDNF are influenced by the intestinal microbiota, as evidenced by changes with antibiotics and experiments involving germ-free mice. Additionally, BDNF secretion is linked to SCFAs and gastrointestinal hormones. (51,52) Diets high in lipids are associated with decreased BDNF levels. (57) Elevated stress can lead to a reduction in BDNF in the hippocampus. (54)

5. Barrier pathways

The gastrointestinal barrier establishes a robust partition between the intestinal tract and the external environment, consequently preserving intestinal homeostasis, through interactions with the gut microbiota and immune cells. When the intestinal barrier is compromised, microbes gain unrestricted entry into the lamina propria and the bloodstream, leading to a condition known as "leaky gut". (58)

The gut microbiota also plays a regulatory role in BBB, situated between the blood vessels and the central nervous system (CNS). Tight junction proteins, specifically occludin, claudin, and junctional adhesion molecules, connect the endothelial cells of the BBB to the cytoskeleton through zona occludens. The BBB also receives support from neighboring astrocytes, microglia, pericytes, neurons, and the extracellular matrix. (59)

The impact of gut microbiota on the integrity of the BBB is substantiated by observed central nervous system (CNS) alterations in germ-free (GF) mice and mice exposed to antibiotics and probiotics. In a recent investigation by Braniste et al., it was revealed that GF mice exhibited heightened BBB permeability and decreased expression of occludin and claudin-5 in various brain regions, including the frontal cortex, hippocampus, and striatum. (52)

Mechanisms: - Discussion of potential mechanisms, such as inflammation, neurotransmitter modulation, and the production of bioactive compounds.

The gut brain axis plays a significant role in influencing various aspects of mental health, including mood disorders in teenagers. Potential connections between the gut-brain axis and mood disorders may involve various mechanisms, including immune response and inflammation, modulation of neurotransmitters, generation of microbial metabolites, regulation of hormones, signalling through the VN, absorption of nutrients, and genetic factors.

Inflammation and immune response:

The gut is a major site of immune system activity, and imbalances in gut microbiota can lead to chronic inflammation. Inflammation, triggered by various factors such as dietary components or microbial imbalance, can stimulate the release of pro-inflammatory cytokines, subsequently influencing the gut-brain axis. Inflammatory signalling between the gut and the brain occurs through three pathways, humoral pathway, cellular immune pathway and neuronal pathway.

In the humoral pathway, intestinal inflammation, triggered by factors like local infection, dysbiosis, or food antigens, initiates the release of proinflammatory cytokines, including IFN-γ, IL-1β, IL-6, and TNF-α. (33,60) If uncontrolled, these circulating factors can compromise the integrity of both the gut-brain barrier (GBB) and BBB, leading to increased intestinal permeability, commonly known as "leaky gut." This phenomenon provides a pathway for certain molecules, toxins, and pathogens from the gut lumen to reach the brain parenchyma, triggering neuroinflammation and associated behavioral changes. For instance, elevated levels of bacterial wall component LPS have been linked to microglial activation, neuronal cell death, cognitive impairment, and sickness behavior mediated by cytokines. (61)

Additionally, SCFAs regulate BBB permeability and microglia function, impacting neuroinflammatory responses. (62) Gut-derived signals, such as tryptophan metabolites, further contribute to regulating both the intestinal barrier and CNS inflammation. (63) The HPA axis also responds to environmental stressors or peripheral responses to intestinal inflammation by releasing glucocorticoids, influencing enteric immune cells, gut function, and microbial composition. (33) Stress-induced dysbiosis can, in turn, activate intestinal inflammation through TH17 cell-dependent release of IL-17A. (64)

B cells in the immune pathway, triggered by gut antigens, transform into IgA-secreting cells for microbial control. In autoimmune nervous system disorders, these cells migrate to the brain, reducing neuroinflammation. Gut-derived cells, influenced by the microbiome, impact CNS immune programming, but in diseases like multiple sclerosis, gut-primed cells exacerbate brain inflammation. Further research is needed to understand how CNS inflammation activates intestinal immune cells and contributes to neuroinflammation. (65,66)

It is interesting to note that shared pro-inflammatory cytokine profiles in the blood occur in both GI disorders and mood disorders, potentially linked to increased intestinal permeability. (67,68)

Changes in prominent microbiome species are noted in Major Depressive Disorder (MDD), Bipolar Disorder (BD), and Post-Traumatic Stress Disorder (PTSD), aligning with reports in inflammatory GI disorders. (69,70) Certain microbiome species, like Lactobacillus spp., are directly related to positive self-judgment, a cognitive process reduced in MDD. (70,71)

Modulation of neurotransmitters

The gut plays a crucial role in producing important neurotransmitters, including 5-HT, dopamine, norepinephrine and GABA, which are essential for regulating mood.

Studies confirm that neurotransmitters serve as mediating pathways in the influence of certain gut microbiota on mental health conditions. Coprococcus consistently showed depletion, corresponding with elevated GABA levels in the blood in individuals with depression. (72) The involvement of Coprococcus and Oscillibacter, two strains associated with depression, includes the promotion of GABA production. (73,74) The consumption of L. plantarum induced changes in emotional behaviors, correlating with increased levels of 5-HT, dopamine, and norepinephrine in the striatum. (75) Lactobacillus strains demonstrated a reduction in anxiety and depression related behaviors through GABA signaling in a mouse model. (22)

Microbial metabolites

The gut microbes produce certain metabolites such as SCFAs, indole compounds, GABA and bile acids.

SCFAs, such as butyrate, acetate, and propionate, are byproducts of microbial fermentation. They have anti-inflammatory properties and can influence neurotransmitter production, impacting mood and behaviour. (45,46, 75)

Indole compounds, produced from the breakdown of tryptophan by certain gut bacteria, play a role in serotonin synthesis. Serotonin is a neurotransmitter linked to mood regulation, and its imbalance is associated with mood disorders like depression. (75,76)

Some gut microbes can produce GABA, an inhibitory neurotransmitter. GABA helps regulate anxiety and stress responses, and alterations in its levels have been linked to mood disorders. (77,78) Bacteroides, a predominant member of the gut microbiota, is a major contributor to the production of gamma-aminobutyric acid (GABA). Through correlation analysis between 16S rRNA sequencing and functional magnetic resonance imaging data, it has been observed that the decreased relative abundance of Bacteroides in the fecal samples of individuals with depression is inversely correlated with depressive symptoms in the brain. (79) The administration of probiotics like Lactobacillus rhamnosus has been used to control the activity of specific GABA genes (GABAB1b and GABAAα2) in different parts of the brain, such as the cortex, hippocampus, and amygdala. This helps improve behaviours associated with anxiety and depression in mice. (22)

Metabolism of bile acids by gut microbes can influence the gut-brain axis, affecting neurological function and potentially playing a role in mood disorders. In a study involving untreated MDD patients, primary and secondary bile acids (BA) were analyzed. The primary BA chenodeoxycholic acid (CDCA) was found to be significantly lower in individuals with severe depression and high anxiety compared to those with milder symptoms. Secondary BAs derived from CDCA, such as lithocholic acid (LCA), were higher in more anxious participants. The study suggests that alterations in BA profiles, indicative of changes in gut microbiome composition, are associated with increased anxiety levels and a higher likelihood of treatment failure in MDD. These findings imply the potential for developing therapies targeting the gut microbiome to address MDD with gut dysbiosis. (80)

Gut hormones

It is widely acknowledged that numerous gut hormones play a crucial role in regulating food intake within the CNS. Interestingly, there exists a frequent coexistence of obesity and mood

disorders. (81) Several gut hormones, including 5-HT, neuropeptide Y, glucagon like peptide-1, cholecystokinin (CCK) and ghrelin, are implicated in mood disorders such as anxiety and depression. (82) For instance, 5-HT, primarily produced by enterochromaffin cells in the gastrointestinal tract, modulates intestinal functions and serves as a neurotransmitter in the CNS influencing mood, sleep, and appetite. (83) The neuropeptide Y family, particularly neuropeptide Y (NPY) and pancreatic polypeptide (PP), affects stress-related disorders and plays a role in the modulation of anxiety and depression through the neuropeptide Y4 receptors. (84) GLP-1, known for stimulating insulin secretion, responds to stress through GLP-1 receptor activation. (85) CCK, abundantly produced in the peripheral nervous system and CNS, regulates food intake and is correlated with increased anxiety-like behaviors. (86) Ghrelin, recognized for its adipogenic effects, also regulates stress response, anxiety, and depression.

Vagus Nerve signaling

Disruption of the gut microbiota has been linked to behaviours resembling depression, potentially influenced by the VN. (87) Inflammation plays a significant role in depression. (88) Vagus nerve stimulation (VNS), an approved treatment for treatment-resistant depression and refractory epilepsy, has the capacity to induce anti-inflammatory cytokines, mitigating inflammation. (89-91) Additionally, VNS offers protection against gut hyperpermeability, preventing the translocation of gut microbiota and reducing the risk of gut and systemic inflammation. (21) It's noteworthy that individuals with depression exhibit a diminished vagal tone. (92)

Absorption of nutrients

Modifications in dietary patterns can impact mood and happiness by influencing the gut microbiome. Studies in mice have demonstrated that alterations in diet account for 57% of variations in the gut microbiome. (93) A pilot study carried out by Martin SE and colleagues revealed that diet modifications involving higher proportions of fat and protein were associated with increased well-being and reduced anxiety and depression, while higher carbohydrate consumption was linked to decreased happiness and heightened anxiety and depression. Additionally, decreased caloric and total fiber intake were associated with increased diversity in the gut microbiome. Furthermore, a correlation was identified, demonstrating that greater diversity in the gut microbiome was associated with decreased anxiety and depression. (94)

Genetic and Epigenetic factors

The genetic makeup of an individual may have the capacity to impact and control the gut microbiota. In a study investigating the influence of genetic variants associated with the gut microbiome on susceptibility to psychiatric disorders such as schizophrenia (SCZ), attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD), and MDD, 201 host genetic markers were examined. Two variants (rs9401458 and rs9401452) were linked to ASD, and one variant (rs75036654) was associated with MDD. The gene-based analysis revealed associations with SCZ (eight genes), MDD (one gene), ADHD (two genes), and ASD (one gene). Furthermore, a gene set comprising 83 genes demonstrated an association with SCZ. These findings suggest that genes associated with microbiome composition may contribute to

influencing the susceptibility of individuals to psychiatric disorders, particularly schizophrenia, with potential implications in ASD, ADHD, and MDD. (95)

Gut microbial products also serve as epigenetic agents, modulating gene regulation and expression. SCFAs exert physiological effects through inhibiting histone deacetylases and binding to G-protein-coupled receptors (GPCRs). SCFAs inhibit histone deacetylases by acetylating lysine residues, promoting the binding of transcription factors to gene promoter regions, and regulating gene expression. (96) Additionally, SCFAs regulate energy metabolism and immune response by activating GPCRs, influencing host molecular signalling. (97,98)

Furthermore, gut microbial products can impact host reactive oxygen species (ROS) production, potentially substituting or mediating ROS levels. ROS, a second messenger, plays a role in altering inflammatory, immune, and signaling processes through oxidative activity on proteins. The interaction between ROS and epigenetic mechanisms involves processes such as histone/protein deacetylation, chromatin remodeling, and transcription factor activation. (99) Increased ROS levels and inflammation induced by certain gut bacteria metabolites contribute to dysregulation of the gut-brain axis, potentially leading to the pathogenesis of mental disorders. Understanding these underlying mechanisms provides valuable insights for improving mental health. (96, 98,99)

Conclusion:

The emerging field of research on the gut-brain axis has shed light on the intricate relationship between microbial influences and adolescent emotions, particularly in the context of mood disorders. Through our exploration, it has become evident that the composition of the gut microbiota plays a significant role in influencing emotional well-being during adolescence.

The bidirectional communication between the gut and the brain underscores the importance of understanding how dietary habits, microbial diversity, and emotional states intertwine. Adolescence, marked by significant developmental changes, presents a critical period during which these interactions can profoundly impact mental health outcomes.

As we navigate the complexities of the gut-brain axis, it is increasingly clear that interventions targeting dietary modifications and microbial balance hold promise in promoting positive emotional health among adolescents. Encouraging diverse, nutrient-rich diets and fostering a healthy gut microbiome may serve as adjunctive strategies in the prevention and management of mood disorders.

Acknowledgements:

All authors thank Nitte(Deemed to be University) for providing facilities to conduct the research.

Authors Contribution:

All authors made equal contributions in the Conception and design, acquisition, analysis and interpretation of the data. All authors approved the final version of the manuscript to be submitted.

Conflict of Interest:

None

REFERENCES

1. Freimer D, Yang TT, Ho TC, Tymofiyeva O, Leung C. The gut microbiota, HPA axis, and brain in adolescent-onset depression: Probiotics as a novel treatment. Brain Behav Immun Health. 2022 Oct 29; 26:100541:1-14.
2. Sagar R, Dandona R, Gururaj G, et al. The burden of mental disorders across the states of India: the global burden of disease study 1990-2017. Lancet Psychiatry. 2020; 7:148–61.
3. Leung CY, Weiss SJ. The gut microbiome of youth who have behavioral and mental health problems: A scoping review. Mental Health & Prevention.2013;31:1-18.
4. McVey Neufeld KA, Luczynski P, Dinan TG, Cryan JF. Reframing the Teenage Wasteland: Adolescent Microbiota-Gut-Brain Axis. Can J Psychiatry. 2016 Apr;61(4):214-21.
5. Agans R, Rigsbee L, Kenche H, Michail S, Khamis HJ, Paliy O. Distal gut microbiota of adolescent children is different from that of adults. FEMS Microbiol Ecol. 2011;77(2):404–12.
6. Yuan X, Chen R, Zhang Y, Lin X, Yang X. Gut microbiota: effect of pubertal status. BMC Microbiol. 2020 Nov 3;20(1):334.1-9.
7. Desbonnet L, Clarke G, Traplin A, O'Sullivan O, Crispie F, Moloney RD et al. Gut microbiota depletion from early adolescence in mice: Implications for brain and behaviour. Brain Behav Immun. 2015 Aug;48:165-73
8. Jamar F, Stärkel P, Windey K, Tremaroli V, Bäckhed F, Verbeke K et al. Intestinal permeability, gut-bacterial dysbiosis, and behavioral markers of alcohol-dependence severity. Proc Natl Acad Sci U S A. 2014 Oct 21;111(42):1-9.
9. Moreno-Indias I, Torres M, Montserrat JM, Sanchez-Alcoholado L, Cardona F, Tinahones FJ et al. Intermittent hypoxia alters gut microbiota diversity in a mouse model of sleep apnoea. Eur Respir J. 2015 Apr;45(4):1055-65.
10. Golubeva AV, Crampton S, Desbonnet L, Edge D, O'Sullivan O, Lomasney KW et al.Prenatal stress-induced alterations in major physiological systems correlate with gut microbiota composition in adulthood. Psychoneuroendocrinology. 2015 Oct;60:58-74.
11. O'Mahony SM, Marchesi JR, Scully P, Codling C, Ceolho AM, Quigley EM et al. Early life stress alters behavior, immunity, and microbiota in rats: implications for irritable bowel syndrome and psychiatric illnesses. Biol Psychiatry. 2009 Feb 1;65(3):263-7.
12. Neufeld LM, Andrade EB, Ballonoff Suleiman A, et al. (2022).Food choice in transition: adolescent autonomy, agency, and the food environment. Lancet 399, 185–197.
13. Meeus W (2016) Adolescent psychosocial development:a review of longitudinal models and research. Dev Psychol 52, 1969–1993.
14. Carson MD, Westwater C, Novince CM. Adolescence and the microbiome. 2023.American Journal of Pathology;193(12):1-10.

15. Shankar V, Gouda M, Moncivaiz J, Gordon A, Reo NV, Hussein L, Paliy O: Differences in gut metabolites and microbial composition and functions between Egyptian and U.S. children are consistent with their diets.2017. mSystems;2(1):1-15.
16. Chakrabarti A, Geurts L, Hoyles L, Iozzo P, 9 AD, La Fata G, et al. The microbiota–gut–brain axis: pathways to better brain health. Perspectives on what we know, what we need to investigate and how to put knowledge into practice. Cellular and Molecular Life Sciences. 2022 Feb;79(2):80.
17. Wang HX, Wang YP. Gut microbiota-brain axis. Chinese medical journal. 2016 Oct 5;129(19):2373-80.
18. Appleton J. The gut-brain axis: Influence of microbiota on mood and mental health. Integrative Medicine: A Clinician's Journal. 2018 Aug;17(4):28.
19. Foster JA, Neufeld KA. Gut–brain axis: how the microbiome influences anxiety and depression. Trends in neurosciences. 2013 May 1;36(5):305-12.
20. Mulak A, Bonaz B. Brain-gut-microbiota axis in Parkinson's disease. World journal of gastroenterology: WJG. 2015 Oct 10;21(37):10609.
21. Bonaz B, Bazin T, Pellissier S. The vagus nerve at the interface of the microbiota-gut-brain axis. Frontiers in neuroscience. 2018 Feb 7;12:49.
22. Liu Y, Forsythe P. Vagotomy and insights into the microbiota-gut-brain axis. Neuroscience research. 2021 Jul 1;168:20-7.
23. Yano JM, Yu K, Donaldson GP, Shastri GG, Ann P, Ma L, Nagler CR, Ismagilov RF, Mazmanian SK, Hsiao EY. Indigenous bacteria from the gut microbiota regulate host serotonin biosynthesis. Cell. 2015 Apr 9;161(2):264-76.
24. Margolis KG, Cryan JF, Mayer EA. The microbiota-gut-brain axis: from motility to mood. Gastroenterology. 2021 Apr 1;160(5):1486-501.
25. Sudo N, Chida Y, Aiba Y, Sonoda J, Oyama N, Yu XN, Kubo C, Koga Y. Postnatal microbial colonization programs the hypothalamic–pituitary–adrenal system for stress response in mice. The Journal of physiology. 2004 Jul;558(1):263-75.
26. Clarke G, Grenham S, Scully P, Fitzgerald P, Moloney RD, Shanahan F, Dinan TG, Cryan J. The microbiome-gut-brain axis during early life regulates the hippocampal serotonergic system in a sex-dependent manner. Molecular psychiatry. 2013 Jun;18(6):666-73.
27. Vagnerová K, Vodička M, Hermanová P, Ergang P, Šrůtková D, Klusoňová P, Balounová K, Hudcovic T, Pácha J. Interactions between gut microbiota and acute restraint stress in peripheral structures of the hypothalamic–pituitary–adrenal axis and the intestine of male mice. Frontiers in immunology. 2019 Nov 19;10:2655.
28. Harno E, Gali Ramamoorthy T, Coll AP, White A. POMC: the physiological power of hormone processing. Physiological reviews. 2018 Oct 1;98(4):2381-430.
29. Sukhareva EV. The role of the corticotropin-releasing hormone and its receptors in the regulation of stress response. Vavilov Journal of Genetics and Breeding. 2021 Mar;25(2):216.
30. Desbonnet L, Garrett L, Clarke G, Bienenstock J, Dinan TG. The probiotic Bifidobacteria infantis: an assessment of potential antidepressant properties in the rat. Journal of psychiatric research. 2008 Dec 1;43(2):164-74.
31. Barouei J, Moussavi M, Hodgson DM. Effect of maternal probiotic intervention on HPA axis, immunity and gut microbiota in a rat model of irritable bowel syndrome. 2012: e46051.

32. Bailey MT, Dowd SE, Galley JD, Hufnagle AR, Allen RG, Lyte M. Exposure to a social stressor alters the structure of the intestinal microbiota: implications for stressor-induced immunomodulation. Brain, behavior, and immunity. 2011 Mar 1;25(3):397-407.
33. Cryan JF, O'Riordan KJ, Cowan CS, Sandhu KV, Bastiaanssen TF, Boehme M, Codagnone MG, Cussotto S, Fulling C, Golubeva AV, Guzzetta KE. The microbiota-gut-brain axis. Physiological reviews. 2019 Aug 28.
34. Rakoff-Nahoum S, Paglino J, Eslami-Varzaneh F, Edberg S, Medzhitov R. Recognition of commensal microflora by toll-like receptors is required for intestinal homeostasis. Cell. 2004 Jul 23;118(2):229-41.
35. Hooper LV, Littman DR, Macpherson AJ. Interactions between the microbiota and the immune system. science. 2012 Jun 8;336(6086):1268-73.
36. Kasarello K, Cudnoch-Jedrzejewska A, Czarzasta K. Communication of gut microbiota and brain via immune and neuroendocrine signaling. Frontiers in Microbiology. 2023 Jan 25;14:1118529.
37. Salvo-Romero E, Stokes P, Gareau MG. Microbiota-immune interactions: from gut to brain. LymphoSign Journal. 2020 Jan 27;7(1):1-23.
38. Duranti S, Ruiz L, Lugli GA, Tames H, Milani C, Mancabelli L, Mancino W, Longhi G, Carnevali L, Sgoifo A, Margolles A. Bifidobacterium adolescentis as a key member of the human gut microbiota in the production of GABA. Scientific reports. 2020 Aug 24;10(1):14112.
39. Allen MJ, Sabir S, Sharma S. GABA Receptor. [Updated 2023 Feb 13]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK526124/
40. Pourhamzeh M, Moravej FG, Arabi M, Shahriari E, Mehrabi S, Ward R, Ahadi R, Joghataei MT. The roles of serotonin in neuropsychiatric disorders. Cellular and molecular neurobiology. 2022 Aug;42(6):1671-92.
41. Spiller R. Serotonin and GI clinical disorders. Neuropharmacology. 2008 Nov 1;55(6):1072-80.
42. Jenkins TA, Nguyen JC, Polglaze KE, Bertrand PP. Influence of tryptophan and serotonin on mood and cognition with a possible role of the gut-brain axis. Nutrients. 2016 Jan;8(1):56.
43. Wikoff WR, Anfora AT, Liu J, Schultz PG, Lesley SA, Peters EC, Siuzdak G. Metabolomics analysis reveals large effects of gut microflora on mammalian blood metabolites. Proceedings of the national academy of sciences. 2009 Mar 10;106(10):3698-703.
44. Hamamah S, Aghazarian A, Nazaryan A, Hajnal A, Covasa M. Role of microbiota-gut-brain axis in regulating dopaminergic signaling. Biomedicines. 2022 Feb 13;10(2):436.
45. Miller TL, Wolin MJ. Pathways of acetate, propionate, and butyrate formation by the human fecal microbial flora. Applied and environmental microbiology. 1996 May;62(5):1589-92.
46. Rutsch A, Kantsjö JB, Ronchi F. The gut-brain axis: how microbiota and host inflammasome influence brain physiology and pathology. Frontiers in immunology. 2020 Dec 10;11:604179.
47. Frost G, Sleeth ML, Sahuri-Arisoylu M, Lizarbe B, Cerdan S, Brody L, Anastasovska J, Ghourab S, Hankir M, Zhang S, Carling D. The short-chain fatty acid acetate reduces appetite via a central homeostatic mechanism. Nature communications. 2014 Apr 29;5(1):3611.

48. Oleskin AV, Shenderov BA. Neuromodulatory effects and targets of the SCFAs and gasotransmitters produced by the human symbiotic microbiota. Microbial ecology in health and disease. 2016 Jan 1;27(1):30971.
49. Nankova BB, Agarwal R, MacFabe DF, La Gamma EF. Enteric bacterial metabolites propionic and butyric acid modulate gene expression, including CREB-dependent catecholaminergic neurotransmission, in PC12 cells-possible relevance to autism spectrum disorders. PLoS One. 2014 Aug 29;9(8):e103740.
50. Silva YP, Bernardi A, Frozza RL. The role of short-chain fatty acids from gut microbiota in gut-brain communication. Frontiers in endocrinology. 2020 Jan 31;11:25.
51. Wishart DS, Feunang YD, Marcu A, Guo AC, Liang K, Vázquez-Fresno R, Sajed T, Johnson D, Li C, Karu N, Sayeeda Z. HMDB 4.0: the human metabolome database for 2018. Nucleic acids research. 2018 Jan 4;46(D1):D608-17.
52. Braniste V, Al-Asmakh M, Kowal C, Anuar F, Abbaspour A, Tóth M, Korecka A, Bakocevic N, Ng LG, Kundu P, Gulyás B. The gut microbiota influences blood-brain barrier permeability in mice. Science translational medicine. 2014 Nov 19;6(263):263ra158-.
53. Erny D, Hrabě de Angelis AL, Jaitin D, Wieghofer P, Staszewski O, David E, Keren-Shaul H, Mahlakoiv T, Jakobshagen K, Buch T, Schwierzeck V. Host microbiota constantly control maturation and function of microglia in the CNS. Nature neuroscience. 2015 Jul;18(7):965-77.
54. Clapp M, Aurora N, Herrera L, Bhatia M, Wilen E, Wakefield S. Gut microbiota's effect on mental health: The gut-brain axis. Clinics and practice. 2017 Sep 15;7(4):987.
55. Alonso C, Vicario M, Pigrau M, Lobo B, Santos J. Intestinal barrier function and the brain-gut axis. Microbial endocrinology: The microbiota-gut-brain axis in health and disease. 2014:73-113.
56. Qin X, Caputo FJ, Xu DZ, Deitch EA. Hydrophobicity of mucosal surface and its relationship to gut barrier function. Shock. 2008 Mar 1;29(3):372-6.
57. Groschwitz KR, Hogan SP. Intestinal barrier function: molecular regulation and disease pathogenesis. Journal of allergy and clinical immunology. 2009 Jul 1;124(1):3-20.
58. Yu S, Sun Y, Shao X, Zhou Y, Yu Y, Kuai X, Zhou C. Leaky gut in IBD: intestinal barrier–gut microbiota interaction. Journal of microbiology and biotechnology. 2022 Jul 7;32(7):825.
59. Bhattarai Y. Microbiota-gut-brain axis: interaction of gut microbes and their metabolites with host epithelial barriers. Neurogastroenterology & Motility. 2018 Jun;30(6):e13366.
60. Gwak MG, Chang SY. Gut-brain connection: microbiome, gut barrier, and environmental sensors. Immune Network. 2021 Jun;21(3).
61. Zhao J, Bi W, Xiao S, Lan X, Cheng X, Zhang J, Lu D, Wei W, Wang Y, Li H, Fu Y. Neuroinflammation induced by lipopolysaccharide causes cognitive impairment in mice. Scientific reports. 2019 Apr 8;9(1):5790.
62. Erny D, Hrabě de Angelis AL, Jaitin D, Wieghofer P, Staszewski O, David E, Keren-Shaul H, Mahlakoiv T, Jakobshagen K, Buch T, Schwierzeck V. Host microbiota constantly control maturation and function of microglia in the CNS. Nature neuroscience. 2015 Jul;18(7):965-77.
63. Scott SA, Fu J, Chang PV. Microbial tryptophan metabolites regulate gut barrier function via the aryl hydrocarbon receptor. Proceedings of the National Academy of Sciences. 2020 Aug 11;117(32):19376-87.

64. Xu C, Lee SK, Zhang D, Frenette PS. The gut microbiome regulates psychological-stress-induced inflammation. Immunity. 2020 Aug 18;53(2):417-28.
65. Botía-Sánchez M, Alarcón-Riquelme ME, Galicia G. B cells and microbiota in autoimmunity. International Journal of Molecular Sciences. 2021 May 3;22(9):4846.
66. Parodi B, Kerlero de Rosbo N. The gut-brain axis in multiple sclerosis. Is its dysfunction a pathological trigger or a consequence of the disease?. Frontiers in Immunology. 2021 Sep 21;12:718220.
67. Abautret-Daly Á, Dempsey E, Riestra S, de Francisco-García R, Parra-Blanco A, Rodrigo L, Medina C, Connor TJ, Harkin A. Association between psychological measures with inflammatory anddisease-related markers of inflammatory bowel disease. International Journal of Psychiatry in Clinical Practice. 2017 Jul 3;21(3):221-30.
68. Xu H, Cao J, Li X, Lu X, Xia Y, Fan D, Zhao H, Ju D, Xiao C. Regional differences in the gut microbiota and gut-associated immunologic factors in the ileum and cecum of rats with collagen-induced arthritis. Frontiers in Pharmacology. 2020 Nov 24;11:587534.
69. Prosberg M, Bendtsen F, Vind I, Petersen AM, Gluud LL. The association between the gut microbiota and the inflammatory bowel disease activity: a systematic review and meta-analysis. Scandinavian journal of gastroenterology. 2016 Dec 1;51(12):1407-15.
70. Doney E, Cadoret A, Dion-Albert L, Lebel M, Menard C. Inflammation-driven brain and gut barrier dysfunction in stress and mood disorders. European Journal of Neuroscience. 2022 May;55(9-10):2851-94.
71. Heym N, Heasman BC, Hunter K, Blanco SR, Wang GY, Siegert R, Cleare A, Gibson GR, Kumari V, Sumich AL. The role of microbiota and inflammation in self-judgement and empathy: implications for understanding the brain-gut-microbiome axis in depression. Psychopharmacology. 2019 May 1;236:1459-70.
72. Valles-Colomer M, Falony G, Darzi Y, Tigchelaar EF, Wang J, Tito RY, Schiweck C, Kurilshikov A, Joossens M, Wijmenga C, Claes S. The neuroactive potential of the human gut microbiota in quality of life and depression. Nature microbiology. 2019 Apr;4(4):623-32.
73. Naseribafrouei A, Hestad K, Avershina E, Sekelja M, Linløkken A, Wilson R, Rudi K. Correlation between the human fecal microbiota and depression. Neurogastroenterology & Motility. 2014 Aug;26(8):1155-62.
74. Liu WH, Chuang HL, Huang YT, Wu CC, Chou GT, Wang S, Tsai YC. Alteration of behavior and monoamine levels attributable to Lactobacillus plantarum PS128 in germ-free mice. Behavioural brain research. 2016 Feb 1;298:202-9.
75. Silva YP, Bernardi A, Frozza RL. The role of short-chain fatty acids from gut microbiota in gut-brain communication. Frontiers in endocrinology. 2020 Jan 31;11:25.
76. Gao K, Mu CL, Farzi A, Zhu WY. Tryptophan metabolism: a link between the gut microbiota and brain. Advances in Nutrition. 2020 May 1;11(3):709-23.
77. Chen Y, Xu J, Chen Y. Regulation of neurotransmitters by the gut microbiota and effects on cognition in neurological disorders. Nutrients. 2021 Jun 19;13(6):2099.
78. Gabbay V, Bradley KA, Mao X, Ostrover R, Kang G, Shungu DC. Anterior cingulate cortex γ-aminobutyric acid deficits in youth with depression. Translational psychiatry. 2017 Aug;7(8):e1216-.
79. Strandwitz P, Kim KH, Terekhova D, Liu JK, Sharma A, Levering J, McDonald D, Dietrich D, Ramadhar TR, Lekbua A, Mroue N. GABA-modulating bacteria of the human gut microbiota. Nature microbiology. 2019 Mar;4(3):396-403.

80. MahmoudianDehkordi S, Bhattacharyya S, Brydges CR, Jia W, Fiehn O, Rush AJ, Dunlop BW, Kaddurah-Daouk R. Gut microbiome-linked metabolites in the pathobiology of major depression with or without anxiety—A role for bile acids. Frontiers in Neuroscience. 2022 Jul 20;16:937906.
81. Milaneschi Y, Simmons WK, van Rossum EF, Penninx BW. Depression and obesity: evidence of shared biological mechanisms. Molecular psychiatry. 2019 Jan;24(1):18-33.
82. Sun LJ, Li JN, Nie YZ. Gut hormones in microbiota-gut-brain cross-talk. Chinese medical journal. 2020 Apr 5;133(07):826-33.
83. Herr N, Bode C, Duerschmied D. The effects of serotonin in immune cells. Frontiers in cardiovascular medicine. 2017 Jul 20;4:48.
84. Verma D, Wood J, Lach G, Herzog H, Sperk G, Tasan R. Hunger promotes fear extinction by activation of an amygdala microcircuit. Neuropsychopharmacology. 2016 Jan;41(2):431-9.
85. Ghosal S, Myers B, Herman JP. Role of central glucagon-like peptide-1 in stress regulation. Physiology & behavior. 2013 Oct 2;122:201-7.
86. Rezayat M, Roohbakhsh A, Zarrindast MR, Massoudi R, Djahanguiri B. Cholecystokinin and GABA interaction in the dorsal hippocampus of rats in the elevated plus-maze test of anxiety. Physiology & behavior. 2005 Apr 13;84(5):775-82.
87. Munshi S. A depressed gut makes for a depressed brain via vagal transmission. Brain, Behavior, and Immunity. 2021 Mar 23;95:15-6.
88. Beurel E, Toups M, Nemeroff CB. The bidirectional relationship of depression and inflammation: double trouble. Neuron. 2020 Jul 22;107(2):234-56.
89. McAllister-Williams RH, Sousa S, Kumar A, Greco T, Bunker MT, Aaronson ST, Conway CR, Rush AJ. The effects of vagus nerve stimulation on the course and outcomes of patients with bipolar disorder in a treatment-resistant depressive episode: a 5-year prospective registry. International journal of bipolar disorders. 2020 Dec;8(1):1-1.
90. Rosas-Ballina M, Olofsson PS, Ochani M, Valdés-Ferrer SI, Levine YA, Reardon C, Tusche MW, Pavlov VA, Andersson U, Chavan S, Mak TW. Acetylcholine-synthesizing T cells relay neural signals in a vagus nerve circuit. Science. 2011 Oct 7;334(6052):98-101.
91. Matteoli G, Gomez-Pinilla PJ, Nemethova A, Di Giovangiulio M, Cailotto C, van Bree SH, Michel K, Tracey KJ, Schemann M, Boesmans W, Berghe PV. A distinct vagal anti-inflammatory pathway modulates intestinal muscularis resident macrophages independent of the spleen. Gut. 2013 Aug 23:gutjnl-2013.
92. Koch C, Wilhelm M, Salzmann S, Rief W, Euteneuer F. A meta-analysis of heart rate variability in major depression. Psychological Medicine. 2019 Sep;49(12):1948-57.
93. Zhang C, Zhang M, Wang S, Han R, Cao Y, Hua W, Mao Y, Zhang X, Pang X, Wei C, Zhao G. Interactions between gut microbiota, host genetics and diet relevant to development of metabolic syndromes in mice. The ISME journal. 2010 Feb;4(2):232-41.
94. Martin SE, Kraft CS, Ziegler TR, Millson EC, Rishishwar L, Martin GS. The Role of Diet on the Gut Microbiome, Mood and Happiness. medRxiv. 2023 Mar 21.
95. Martins-Silva T, Salatino-Oliveira A, Genro JP, Meyer FD, Li Y, Rohde LA, Hutz MH, Tovo-Rodrigues L. Host genetics influences the relationship between the gut microbiome and psychiatric disorders. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2021 Mar 2;106:110153.

96. Zhu J, Zhao N, Chen Y, Zhu L, Zhong Q, Liu J, Chen T. Sodium butyrate modulates a methamphetamine-induced conditioned place preference. Journal of neuroscience research. 2017 Apr;95(4):1044-52.
97. Koh A, De Vadder F, Kovatcheva-Datchary P, Bäckhed F. From dietary fiber to host physiology: short-chain fatty acids as key bacterial metabolites. Cell. 2016 Jun 2;165(6):1332-45.
98. Ohira H, Tsutsui W, Fujioka Y. Are short chain fatty acids in gut microbiota defensive players for inflammation and atherosclerosis?. Journal of atherosclerosis and thrombosis. 2017 Jul 1;24(7):660-72.
99. Doenyas C. Potential role of epigenetics and redox signaling in the gut–brain communication and the case of autism spectrum disorder. Cellular and Molecular Neurobiology. 2022 Mar;42(2):483-7.