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# Adolescent Refractory Anxiety Disorders Rising: Gut Microbiota-Associated Metabolites to The Rescue?

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## ABSTRACT

This review provides a comprehensive analysis of the gut microbiota and its associated metabolites in relation to stress and anxiety disorders, with a specific focus on adolescents. It addresses the dearth of information regarding the composition of microbiota-associated metabolites that have the potential to effectively alleviate anxiety and stress disorders in this age group. Adolescence is a vulnerable period characterized by hormonal, physiological, emotional, and environmental changes, making individuals more prone to psychiatric disorders that manifest as stress and anxiety. However, treatment is challenging due to patient non-compliance, particularly in refractory cases, necessitating tailored interventions. The gut microbiota, a vast community of microorganisms residing in the gastrointestinal system, plays a crucial role in influencing brain function through the microbiota-gut-brain axis (MGBA). Understanding the role of the gut microbiota in stress and anxiety disorders has opened avenues for potential targeted and innovative therapeutic approaches. This review consolidates the existing knowledge about gut microbiota and associated metabolites implicated in stress and anxiety disorders in adolescents. Through an extensive literature review, we compile a comprehensive list of microorganisms and metabolites known to alleviate symptoms of these disorders. The identification of microbiota-associated metabolites with the potential to ameliorate stress and anxiety disorders in adolescents can bridge the knowledge deficit and contribute to the development of novel treatment strategies and interventions, including unconventional approaches such as fecal microbiota transplantation (FMT).

## Introduction

Adolescence, the phase of human life between ages 10 to 19 (as described by WHO) is the bridge that connects childhood to adulthood. This very unique phase of life is influenced by one's childhood, and is responsible for laying the foundations of one's adulthood. Tremendous hormonal and physiological changes, including developmental changes in the brain occurring at a very rapid pace are hallmarks of adolescence. External stressors such as peer pressure and identity crisis add to the challenges significantly. Consequently, stress and anxiety disorders often manifest first during adolescence (McVey Neufeld, Luczynski, Seira Oriach, et al., 2016; Paus et al., 2008; Simkin, 2019). Notwithstanding the availability of therapeutic measures that are effective in most cases of stress and anxiety disorders, the burden of refractory cases that do not respond to conventional therapeutic measures is undebatable. Additionally, the conventional therapeutic measures aren't necessarily tailor-made to address the specific needs of the adolescent age group.

The immense population of commensal microorganisms inhabiting the human gastrointestinal system, collectively known as the gut microbiota heavily influence many functional aspects of the human brain. The gut microbiota and the brain form a bidirectional communication pathway known as the microbiota-gut-brain axis (MGBA), which is known to significantly influence the pathophysiology of stress and anxiety disorders

(Cryan, 2016; Foster et al., 2017a; Izuno et al., 2021; Malan-Muller et al., 2018a; Simpson et al., 2021; Wiley et al., 2017; Yarandi et al., 2016a). The microbiome comprises of a collection of microorganisms that are unique to every individual, and the gut microbiota is a subset of their microbiome that exists in the gut. The gut microbiota is influenced by age, dietary preferences, and lifestyle choices. This results in certain similarities in the gut microbiota of individuals belonging to a particular age group, ethnicity, or community. Therefore, gut-microbiota-based therapeutic approaches have the potential to be tailor-made for the needs of patient groups that share certain commonalities. This makes such approaches ideal for treating disorders affecting adolescents (Cohen Kadosh et al., 2021; Simkin, 2019; Yahfoufi et al., 2020a).

Currently, research that explores the therapeutic efficacy of the gut microbiota in stress and anxiety disorders focuses on improving the availability of beneficial microbes either through dietary and lifestyle changes or through the intake of beneficial probiotics and prebiotics (Foster et al., 2017a; Izuno et al., 2021; Taylor & Holscher, 2020a). However, these treatment methods demand prolonged adherence and co-operation from the patient, a formidable challenge when dealing with adolescents. Cultural differences that affect food preferences and eating habits also impede the implementation and success of these treatment methods. The fluctuant nature and prolonged duration of treatment make it ineffective in severe and refractory cases. Additionally, there is a dearth of research that defines the composition of microbiota-associated metabolites with the potential to effectively ameliorate anxiety and stress disorders in adolescents.

In this review, we collate existing information about gut microbiota and metabolites associated with psychiatric disorders from an exhaustive review of relevant literature. We begin by summarizing the effects of dysbiosis on the nervous system, the immune system, and the endocrine system. Although dysbiosis affects several organ systems, our review emphasizes on these three systems because of their predominant role during the adolescent phase of life. Further, we discuss the factors contributing to the increased vulnerability of the adolescent age group to psychiatric disorders. Next, we generate a comprehensive list of microbiota-associated metabolites found to alleviate symptoms of stress and anxiety disorders and describe their individual roles, with special emphasis on adolescents. Then, we outline the existing treatment strategies and interventions for stress and anxiety disorders in adolescents. Last, we discuss the potential of the indicated microbiota-associated metabolites in ensuring targeted and effective treatment. In addition to conventional treatment strategies, we also expect unconventional but promising alternatives such as FMT that are being explored for the treatment of psychiatric disorders to benefit immensely from the findings of this study.

## Microbiota-Gut-Brain Axis: A Functional Extension of the Gut-Brain Axis

The gastrointestinal tract (GIT) and the central nervous system (CNS) interact via a bidirectional communication pathway referred to as the gut-brain axis (GBA). This axis of communication is involved in complex interactions with the nervous system, the immune system, the digestive system, the endocrine system, and even metabolic pathways. The interactions among the microorganisms present in the gut, collectively known as the gut microbiota, and the gut epithelium play a very important role in the functioning of the gut-brain axis. This has resulted in this axis of communication being extended to include the gut microbiota, and therefore referred to as the microbiota-gut-brain axis (MGBA).

### Gut Microbiota and Its Composition

The gut microbiota comprises of a diverse community of trillions of microorganisms including bacteria, viruses, and fungi that reside within the human gastrointestinal system. This community of microorganisms is a subset of the huge population of commensal organisms that inhabit the human body, and has a composition that is complex and varies between individuals. The gut is predominantly inhabited by microorganisms that are vital for maintaining optimal gut health, such as those primarily belonging to microbial phyla including Firmicutes,

Bacteroidetes, Actinobacteria, and Proteobacteria. Factors such as age, diet, genetics, and environmental influences shape the composition of the gut microbiota (Flint et al., 2012).

Interactions among different microbial species within the gut microbiota are crucial for its proper functioning. Beneficial microbes help prevent the colonization of harmful pathogens through cooperative and competitive interactions. The gut microbiota contributes to overall health by producing essential vitamins, breaking down dietary fiber, and metabolizing nutrients to produce short-chain fatty acids (SCFAs). The development and maturation of the immune system are also influenced by the gut microbiota (Round & Mazmanian, 2009).

Various factors including diet, antibiotics, stress, and lifestyle choices can alter the gut microbiota. Lifestyle choices like a balanced diet and regular physical activity can support its diversity and balance. Imbalances in the gut microbiota, known as dysbiosis, have systemic implications and contribute to health conditions (Fan & Pedersen, 2021).

## Dysbiosis

Microbiota-associated metabolites and products, neurotransmitters, and gut hormones form a network of pathways that facilitate the effective functioning of the MGBA (De Vadder et al., 2014; Hooks et al., 2020; Schippa & Conte, 2014; Yarandi et al., 2016b). During adolescence, internal and external stressors such as long-term consumption of low nutritive value foods, erratic sleep schedules, alcohol and drug abuse, frequent infections precipitating the indiscriminate use of antibiotics, surging pubertal hormones, and stress-inducing situations such as academic and peer pressure disturb the composition and distribution of the gut microbiota. This results in an imbalance of the gut microbiome, termed as dysbiosis (Paus et al., 2008; Yahfoufi et al., 2020a). Stress and anxiety disorders have been linked to alterations in the gut microbiota composition, such as reduced microbial diversity and imbalanced distribution of microorganisms. In addition to the digestive system, dysbiosis also affects other organ systems and pathways, of which the effects on the nervous, immune, and endocrine systems notably impact the development of several psychiatric disorders (Westfall et al., 2017).

### *Effects Of Dysbiosis On The Nervous System*

Neurotransmitters such as gamma-aminobutyric acid (GABA), serotonin, and dopamine regulate mood, cognition, and behavior. Dysbiosis disrupts the production of these neurotransmitters, thereby resulting in a spectrum of psychiatric illnesses (Barrett et al., 2012; Clapp et al., 2017a; Cryan & Dinan, 2012; Dinan & Cryan, 2013; Foster & McVey Neufeld, 2013; Simkin, 2019), of which adolescents are the most vulnerable to stress and anxiety disorders. Increased manifestation of anxiety symptoms has been linked to low serotonin levels demonstrating the direct role of neurotransmitter levels in management of anxiety and stress (Chen et al., 2021a; Dinan & Cryan, 2012; Foster et al., 2017b; Helton & Lohoff, 2015; Rogers et al., 2016). GABA is an inhibitory neurotransmitter that mediates a signaling pathway responsible for facilitating anxiety regulation. Dysbiosis impairs GABA production, metabolism, and signaling, thereby disrupting GABA-mediated neural transmission and causing heightened anxiety symptoms and altered stress responses (Chen et al., 2021a).

Dysbiosis triggers uncontrolled immune responses in the gut that precipitate a chronic systemic inflammatory state, including neuroinflammation. Proinflammatory molecules interfere with neurotransmitter secretion and disrupt the delicate balance required for the optimal functioning of neurotransmitters. Chronic inflammatory conditions negatively impact neuronal function, and exacerbate stress and anxiety disorders (Clapp et al., 2017b; Evrensel et al., 2020). Synergy among the gut microbiota is key for the integrity of the gut barrier and regulates gut permeability. Loss of this synergy impairs gut barrier function disrupting the GBA and permitting the unrestricted entry of toxins, proinflammatory molecules, and microbial components into the bloodstream. Once in the bloodstream, these molecules have the potential to breach the blood-brain-barrier (BBB) and trigger neuroinflammatory processes (Kociszewska & Vlajkovic, 2022).

Stress responses are regulated by the hypothalamic-pituitary-adrenal (HPA) axis. Gut microbiota contributes to the development of the HPA axis early in life, thereby influencing stress response patterns throughout life (Malan-Muller et al., 2018b). Factors altering the HPA axis demonstrate direct links to adolescent mental health problems. The possibility of leveraging the HPA axis to predict the emergence and persistence of adolescent mental health problems has also been proposed (Marceau et al., 2015). Dysbiosis is deleterious to the regulation of the HPA axis, and augments stress and anxiety symptoms (Frankiensztajn et al., 2020a; Huo et al., 2017).

The development of neural networks, ability to learn, and manage stress responses is a combined function of the generation of new neurons known as neurogenesis and the strengthening of neural connections, an ability of neurons known as synaptic plasticity. Dysbiosis compromises neurogenesis and impairs neural plasticity, thereby increasing vulnerability to stress and anxiety disorders (C. Liu et al., 2022; Murciano-brea et al., 2021).

### *Effects of Dysbiosis On the Immune System*

Interactions of the gut microbiota and the immune system are very precarious, and even the slightest dysregulation of the gut microbiota often activate inflammatory pathways. Dysbiosis-induced modulation of the immune system has been implicated in several neurological disorders.

Maintenance of immune homeostasis is crucial for keeping a check on inflammatory processes. Regulatory T cells (Tregs) and certain immune cells that produce anti-inflammatory cytokines prevent unwarranted inflammation. However, dysbiosis upsets immune homeostasis by altering the distribution and activity of these cell populations in the gut and peripheral tissues. Changes in gut microbiota also trigger the production of proinflammatory chemicals that hypersensitize the immune system. This results in hyperactivity of the immune system leading to a systemic inflammatory state. Inflammatory pathways impact the normal functioning of the immune system, thereby affecting optimal functioning of various organ systems. Dysregulated immune responses also affect the ability of the immune system to differentiate between self and non-self. Autoimmune and degenerative diseases are often a result of such rogue functioning of the immune system. Malfunctioning immune systems and effects of such systemic inflammation on the nervous system often manifest as symptoms of stress and anxiety disorders (Cruz-Pereira et al., 2019).

The integrity of the intestinal barrier is crucial for restricting the entry of microorganisms and microbial products into the bloodstream. Well-balanced and healthy gut microbiota keeps this barrier intact, thus ensuring safety of the other organ systems. However, dysbiosis can compromise this barrier and result in a hyperpermeable intestine, aka ‘leaky gut’. Hyperpermeability of the intestine in turn compromises the integrity of the blood-brain-barrier, thus providing access to the CNS and triggering an influx of immune cells. Neuroinflammation resulting from this could potentially contribute to stress and anxiety (Kociszewska & Vlajkovic, 2022).

The optimal functioning of the immune system also reflects on neuronal function and neurotransmitter signaling. Cytokines and chemokines produced and released by the immune cells act as signaling molecules that can affect the metabolism of neurotransmitters. Dysbiosis-induced malfunctioning of the immune system, therefore, has a direct effect on the signaling pathways important for mood and anxiety regulation. Hence, immune-mediated alteration of neurotransmission can contribute to the pathogenesis of stress and anxiety disorders (Balan et al., 2021).

Dysbiosis-induced immune dysregulation can increase sensitivity to various internal and external stressors. The immune system interacts with the neuroendocrine system and the HPA axis to modulate stress responses. Dysbiosis has the potential to disrupt this interaction and manifest as heightened stress responses and increased vulnerability to stress and anxiety disorders (Frankiensztajn et al., 2020b; McCormick & Mathews, 2007; Misiak et al., 2020).

The exchange of signals, molecules, and metabolites between microorganisms and the various cells, tissues, and organs forms a bidirectional pathway of communication, known as microbial-host crosstalk. This

communication pathway is influenced by direct cell-to-cell contact, secretion of signaling molecules, and modulation of host immune responses. Gut microbiota is an essential component of the microbial-host crosstalk. Dysbiosis can, therefore, impair immune modulation and disrupt immune responses. This has a deleterious effect on the interactions of the gut microbiota and the immune system, which compromise stress and anxiety responses in adolescents (Bibbò et al., 2022; Choi et al., 2020; Du et al., 2020).

### *Effects of Dysbiosis On the Endocrine System*

An optimally functioning HPA axis is indispensable for appropriate stress responses. The activity of the HPA axis is influenced by several factors, especially the hormonal environment and the gut microbiota. Compromised gut health, therefore, directly affects the ability to manage and respond appropriately to stress. Balanced hormone levels are crucial for the optimal functioning of the HPA axis. Imbalances in the levels of certain hormones, such as cortisol, serotonin, and dopamine have been implicated in increased vulnerability to anxiety disorders in adolescents (McCormick & Mathews, 2007; Misiak et al., 2020).

Serotonin, aka the 'feelgood' neurotransmitter, gets its name for its role in mood regulation and cognitive function. A large percentage of the serotonin level in the body is produced in the gut, and therefore the gut microbiota plays a key role in the metabolism of serotonin. Alterations in the gut microbiota can disrupt these metabolic processes, and cause imbalances in the neurotransmitter levels. Imbalanced levels and altered metabolism of neurotransmitters, especially that of serotonin may contribute to anxiety symptoms (Chen et al., 2021b; Helton & Lohoff, 2015; F. Huang & Wu, 2021; Sjöstedt et al., 2021).

Mood regulation and anxiety management are also managed by thyroid hormones and gonadal hormones such as estrogen, progesterone, and testosterone, which are metabolized and regulated by the gut microbiota. Dysbiosis can disrupt the balance and metabolism of these hormones. Thyroid hormones play a central role in metabolism, regulation of body temperature, and protein synthesis processes. Therefore, impaired functioning of these hormones affects several organ systems and compromise optimal physiological functioning and metabolism. Dysbiosis-induced alterations in the levels and functions of these hormones are known to cause irregular mood patterns, fluctuating energy levels, and increased manifestations of anxiety, stress, and depressive symptoms (Fröhlich & Wahl, 2019; Knezevic et al., 2020; Maeng & Beumer, 2023; Sovijit et al., 2021).

Insulin, a hormone crucial for blood sugar regulation, can impact mood regulation and anxiety symptoms. Dysbiosis disrupts insulin regulation, alterations in insulin sensitivity, and glucose metabolism. Dysregulated insulin levels and signaling pathways, in turn, have been implicated in the development or exacerbation of stress and anxiety disorders (Soto et al., 2018).

The growth hormone is important for optimal growth, metabolism, and stress responses. Gut microbiota plays an important role in the secretion and regulation of the growth hormone (C. Huang et al., 2023). Dysbiosis impacts the delicate balance of this hormone, its metabolism, and signaling pathways (Jensen et al., 2020), thereby contributing to exacerbated stress and anxiety symptoms.

## Adolescence: A Phase Vulnerable to Stress and Anxiety Disorders

### Hormonal, Physiological, Emotional, and Environmental Changes

Adolescence is a dynamic and transformative period characterized by a multitude of changes that encompass hormonal, physiological, emotional, and environmental aspects (Jaworska & MacQueen, 2015). The onset of puberty triggers the production of reproductive hormones such as estrogen and testosterone resulting in significant hormonal fluctuations, which in turn contribute to physical transformations like growth spurts, development of secondary sexual characteristics, and changes in body composition (Marceau et al., 2015).

Various body systems mature and undergo significant physiological changes during this phase. The growth spurts require the skeletal system to undergo rapid bone development and restructuring, while the increased demand for blood supply results in growth and increased efficiency of the cardiovascular system. The processes of rewiring and elimination of excess synapses, known as synaptic pruning that occur in the neurological system are crucial for enhanced cognitive functions and decision-making abilities that prepare the individual for adulthood (Barnea-Goraly et al., 2005; Benes, 1989; Giorgio et al., 2010; Konrad et al., 2013; Sturman & Moghaddam, 2011). Heightened emotional sensitivity and the emergence of a more complex range of emotions that can be attributed to the interplay between hormonal changes, brain development, and social factors are common experiences in this age group. Additionally, struggles related to identity formation, family dynamics, self-esteem issues, increased peer influence, and societal expectations further contribute to emotional fluctuations and cause adolescents to hyper-focus on social relationships (Brizio et al., 2015; Gardner & Steinberg, 2005; Spear, 2011).

The adolescent phase is crucial to the development of coping mechanisms that help in the process of dealing with stressors later in life (Crone & Dahl, 2012; Romeo, 2010). Therefore, insights into the reasons that make this phase particularly vulnerable to stress and anxiety disorders (Leussis & Andersen, 2008) are important for the development of new strategies for the treatment of stress and anxiety disorders, especially for refractory cases.

## Factors Contributing to Increased Susceptibility to Stress and Anxiety Disorders

Psychiatric disorders often manifest during the adolescent phase of life (McVey Neufeld, Luczynski, Dinan, et al., 2016). Certain key factors make adolescents extremely vulnerable to developing psychiatric disorders, especially those that manifest as stress and anxiety disorders.

### *Brain Development*

The nervous system and particularly the brain undergoes significant structural and functional changes during adolescence. The prefrontal cortex of the brain that plays a central role in decision-making and impulse control undergoes substantial remodeling during this phase. Extensive synaptic pruning that occurs in the prefrontal cortex during adolescence may temporarily disrupt its maturation. Myelination, the process of formation of a fatty sheath called myelin around nerve fibers, which enhances the speed and efficiency of neural communication also takes longer to complete in the prefrontal cortex as compared to the other regions of the brain, thus contributing to the maturation lag. Intrinsic factors such as hormonal influences and extrinsic factors such as stress and exposure to substances like alcohol or drugs impact brain development and potentially contribute to a lag in the maturation of the prefrontal cortex. Relative slow maturation of the prefrontal cortex has been implicated in impulsivity and emotional dysregulation seen in adolescents (Blakemore & Choudhury, 2006; Eiland & Romeo, 2013; Giedd, 2009; Giedd et al., n.d., 1999; Goddings et al., 2014; Keshavan et al., 2014; Konrad et al., 2013; Paus et al., 2008; Sowell et al., 2001; Sturman & Moghaddam, 2011).

### *Hormonal Changes*

Adrenal and gonadal hormones, such as cortisol, testosterone, and estrogen, play a significant role in shaping mental health outcomes during adolescence. There is an intense surge of sex hormones, such as estrogen and testosterone during the pubertal years. These profound hormonal changes impact brain development and affect the regulation of emotions and stress. The fluctuant nature of the hormonal changes influences emotional reactivity, mood regulation, reward processing, cognitive processes, and social behavior, which are relevant factors in stress and anxiety disorders (Marceau et al., 2015; Romeo & Romeo, 2003). Stress-responsive hormones, particularly cortisol, can influence the stress response system and contribute to the development of anxiety disorders (Schmidt et al., 2015). Heightened cortisol levels, combined with other factors like genetic predispo-

sition and environmental stressors, can increase the risk of anxiety-related problems in adolescents. The complex interplay between hormonal changes and psychosocial factors, such as family environment, peer relationships, and stress exposure, further modulate the risk for stress and anxiety disorders in this vulnerable population (Blakemore & Choudhury, 2006; Brizio et al., 2015; Crone & Dahl, 2012; Leussis & Andersen, 2008). Therefore, the dynamics of the adrenal and gonadal hormones during adolescence is a significant factor in increasing the vulnerability of adolescents to the development of stress and anxiety disorders.

### *Sensitivity to Social and Environmental Factors*

Adolescence is a time of heightened sensitivity to social and environmental influences, which can significantly impact mental health outcomes. The desire for social acceptance, peer relationships, societal expectations, and the impact of social interactions can significantly influence mental health and emotional well-being. Additionally, exposure to adverse life events, such as trauma, neglect, dysfunctional family dynamics, or chronic stress during this sensitive period can increase the risk of developing psychiatric disorders. Identity crisis, discrepancies between one's own self-image and social expectations, and the need to fit in and conform to social norms can lead to heightened stress levels and anxiety. The interplay between sensitivity to social and environmental factors and the ongoing brain development during adolescence can amplify the impact of these influences on mental health outcomes. The heightened sensitivity to social and environmental cues, combined with the malleability of the developing brain, creates a unique vulnerability for stress and anxiety disorders during this stage. Promoting positive social relationships, providing a supportive and nurturing environment, and addressing adverse experiences and stressors have proven to be crucial means to mitigate the risk of stress and anxiety disorders during this sensitive period (Blakemore & Choudhury, 2006; Brizio et al., 2015; Crone & Dahl, 2012; Leussis & Andersen, 2008; Paus et al., 2008).

### *Genetic and Environmental Interactions*

Genetic predispositions interact with environmental factors to influence the development of psychiatric disorders. Adolescence is a critical period for gene-environment interactions, where genetic vulnerabilities may be triggered by specific environmental factors, such as family dysfunction, peer pressure, or substance abuse. While certain genetic variations may increase the risk, genetics alone do not determine the outcome. Environmental factors, such as early life adversity, family dynamics, and exposure to chronic stress, can modify the expression of genes related to stress response and emotional regulation. The dynamic changes in brain structure and function during adolescence also contribute to the increased susceptibility to stress and anxiety disorders (Chubar et al., 2020; Kwong et al., 2019; Lau et al., 2007; Ollmann et al., 2021; Stein et al., 2008).

## Challenges in Implementing Existing Therapeutic Measures

Stress and anxiety disorders are multifaceted conditions that often involve a combination of biological, psychological, and environmental factors. Treatment of these disorders is thus perplexing and challenging. Standard treatment approaches, such as medication and psychotherapy, may not yield the desired results in all individuals. Refractory cases refer to individuals who do not respond adequately to standard treatment approaches. The complexity of these disorders can make it challenging to identify the most effective treatment strategies for refractory cases (Bokma et al., 2019; Roy-Byrne, 2015).

While most cases of stress and anxiety disorders are reported among adolescents, the unique nature and complexities associated with patients in this age group often challenge the treating clinician. The physiological and psychosocial dynamics impacting this population also precipitate in a higher occurrence of refractory cases. Patient non-compliance or non-cooperation is rampant among adolescent patients due to low motivation levels, inability to understand the importance of treatment, or struggles associated with expression of symptoms. These result in resistance to therapy, inconsistent adherence to medication or therapeutic regimens,

or a lack of engagement in therapeutic activities, thus hindering treatment effectiveness and limiting positive outcomes. The heterogeneous nature of stress and anxiety disorders necessitates tailored interventions that address the unique needs and underlying factors contributing to refractory symptoms (Chiu et al., 2016; Herpers et al., 2021).

The lack of comprehensive understanding of the intricate interplay of genetic, environmental, and neurochemical factors that contribute to treatment resistance in refractory cases of stress and anxiety disorders further complicates treatment efforts. The current knowledge gaps limit the development of targeted interventions specifically designed for refractory cases. Some innovative approaches, such as neuromodulation techniques like transcranial magnetic stimulation or deep brain stimulation and novel pharmacological agents, have shown promise in addressing refractory cases. However, these interventions are still in experimental stages and require further research to establish their safety, efficacy, and long-term outcomes. Meanwhile, a combination of personalized treatment plans, involving psychotherapy, medication adjustments, increased intake of prescribed or food-derived probiotics and prebiotics, lifestyle modifications, and alternative therapies form the mainstream treatment plan (Al-Harbi, 2012; Ansara, 2020; Garakani et al., 2020a; Otto et al., n.d.).

## Gut Microbiota-Associated Metabolites to The Rescue

### Influence of Gut Microbiota-Associated Metabolites On the Gut-Brain Axis

The gut microbiota and the gut-brain axis interact via the microbiota-gut-brain axis, and affect various aspects of human health. The gut-microbiota are associated with a wide array of metabolites, which are small molecules produced as a byproduct of metabolic activities. These microbiota-associated metabolites facilitate the interaction of the microbiota with the gut-brain axis. These metabolites have the ability to interact with the host's cells and systems, including those within the CNS, and can exert various physiological effects.

The influence of microbiota-associated metabolites on the gut-brain axis is multifaceted. They can modulate neurotransmitter synthesis and signaling, affect neuroinflammation and immune responses, influence the integrity and permeability of the gut barrier, and even impact gene expression within the brain. These effects can have profound implications for brain function, behavior, and mental health.

Due to their interactions with the nervous system, microbiota-associated metabolites are being extensively investigated for gaining insights into neuropsychiatric disorders, including anxiety, depression, and neurodevelopmental disorders. These metabolites are promising candidates for novel targeted therapeutic approaches, especially in the treatment of refractory psychiatric cases.

### Gut Microbiota-Associated Metabolites That Impact Stress and Anxiety Disorders

In this study, we have compiled research conducted on the impact of the gut microbiota and microbiota-associated metabolites in mitigating stress and anxiety disorders. We collected relevant studies from academic databases using specific keywords and phrases including microbiota-associated metabolites, gut microbiota, stress disorders, anxiety disorders, gut-brain axis, microbial metabolites, adolescents, and therapeutic approaches. While not all of the included studies focus specifically on adolescents, the majority of them are centered around this age group.

Based on this compilation of nearly 50 relevant studies, we generated a comprehensive list of microbiota-associated metabolites that have been shown to ameliorate stress and anxiety disorders.

### *Gamma-Amino Butyric Acid*

Gamma-amino butyric acid (GABA) is an inhibitory neurotransmitter in the CNS. It helps to regulate and reduce neuronal activity in the brain and plays a crucial role in maintaining, thereby ensuring proper brain function. Gut microbiota converts the amino acid glutamate to produce GABA using the enzyme glutamate decarboxylase through the process of decarboxylation.

The *Bifidobacterium* and *Lactobacillus* families are associated with GABA production and expression in the brain. Specific strains such as *L. brevis* and *B. dentium* have been found to increase GABA concentrations both *in vitro* and *in vivo*. *L. rhamnosus* derived GABA expression levels have been shown to vary in different regions of the brain, although overall *L. rhamnosus* reduced the levels of stress-induced corticosterone and ameliorated anxiety- and depression-related behavior (Barrett et al., 2012; Bravo et al., 2011; Janik et al., 2016).

The time lag between the intervention and measurable effects on GABA levels has been found to be comparable to that required by serotonin-reuptake inhibitors (SRIs), which are commonly prescribed antidepressant medications (Kodish, 2011). This implies that novel therapeutic approaches targeting GABA may potentially take the same time frame to show effects as the conventional methods, while ensuring a more specific and targeted approach. These findings highlight the potential of certain bacterial strains, particularly those within the *Lactobacillus* family, to modulate GABA levels in the brain and influence anxiety-related behaviors.

### *Kynurenine*

Kynurenine, an amino acid metabolite that plays a significant role in the tryptophan metabolism pathway is produced from the essential amino acid tryptophan through the action of the enzyme tryptophan 2,3-dioxygenase (TDO) or indoleamine 2,3-dioxygenase (IDO). While the majority of kynurenine synthesis occurs through enzymatic conversion of tryptophan in host tissues, certain bacterial species in the gut microbiota also possess the enzymes necessary for kynurenine production. Certain strains of *Escherichia coli* and *Lactobacillus* species, have been found to express the enzyme tryptophanase, which can convert tryptophan into indole, which in turn, can be further metabolized by host enzymes to produce kynurenine.

Once tryptophan is converted into kynurenine, it can follow different metabolic pathways. One major pathway is the kynurenine pathway, where kynurenine is further metabolized into various downstream metabolites, including kynurenic acid, quinolinic acid, and anthranilic acid. These metabolites have diverse functions and can exert both neuroprotective and neurotoxic effects in the CNS. Kynurenine and its metabolites have been implicated in numerous physiological and pathological processes, including immune regulation, inflammation, neurodegeneration, and neuropsychiatric disorders. The balance between different branches of the kynurenine pathway, particularly the levels of neuroprotective and neurotoxic metabolites, is crucial for maintaining proper brain function and mental well-being. Imbalances in this pathway, with an increased production of neurotoxic metabolites or a deficiency of neuroprotective metabolites, have been proposed to contribute to the development of psychiatric symptoms.

The interplay between host tryptophan metabolism and microbial tryptophan metabolism, including kynurenine production, is complex and can have implications for immune regulation, neuroinflammation, and neuropsychiatric disorders. Studies investigating the impact of antibiotic administration during young adulthood in mice on various aspects of brain function and gene expression indicate a reduction in kynurenine levels although high levels of serum tryptophan are maintained. The expression of hippocampal brain-derived neurotrophic factor (BDNF) messenger RNA (mRNA), a protein essential for neuronal growth and plasticity also showed significant decrease. The antibiotic treatment was also implicated in alterations in the levels of brain monoamines and their metabolites, hypothalamic oxytocin, and vasopressin mRNA expression (Desbonnet et al., 2015; Heijtz et al., 2011). These findings indicate that manipulating the gut microbiota through antibiotic administration during adolescence can have enduring effects on brain function and gene expression. Altered levels of kynurenine and its metabolites have been observed in individuals with psychiatric conditions including anxiety and depression (Savitz, 2017), suggesting a potential role in their pathophysiology.

### *Tryptophan*

Tryptophan is one of the nine essential amino acids that cannot be produced by the human body and must be obtained through the diet. It serves as a building block for the production of important molecules in the body, including proteins, neurotransmitters, and signaling molecules. While the gut microbiota does not directly produce tryptophan, certain microbial species including *Lactobacillus rhamnosus*, *Lactobacillus reuteri, Bifidobacterium infantis,* and *Bifidobacterium longum*, influence the availability and utilization of tryptophan. On the other hand, certain microbial species including *Escherichia coli*, *Clostridium sporogenes*, and *Proteus mirabilis* possess the enzyme tryptophanase, which allows them to break down tryptophan for their own metabolic needs. Dysbiosis resulting in colonization of the gut by these microbes creates a conducive environment for these microbes to compete for tryptophan, thereby compromising its bioavailability (M. Liu et al., 2022).

Tryptophan plays a crucial role in the synthesis of serotonin, a neurotransmitter involved in mood regulation, sleep-wake cycles, and appetite control. Additionally, tryptophan is a precursor for the synthesis of other important compounds such as melatonin, niacin (vitamin B3), and kynurenine. The kynurenine arm of the tryptophan pathway generates metabolites that have both neuroprotective and neurotoxic implications. Therefore, an imbalance in tryptophan levels can percolate to a dysfunctional kynurenine pathway precipitating in various psychiatric manifestations. Anhedonia, the inability to enjoy activities that an individual normally would, often manifests in various psychiatric conditions including anxiety and stress disorders. Increased levels of pro-inflammatory cytokines induce the inflammatory kynurenine pathway causing tryptophan to break down into neurotoxins that alter the CNS, and has been associated with anhedonia (Freed et al., 2019).

Tryptophan depletion has been implicated as a risk factor for depression incidences as per LEIDS-r scores, which is a self-report questionnaire that measures vulnerability to depression (Steenbergen et al., 2015). Alcohol abuse, often seen among adolescents has the potential to compromise the gut barrier integrity causing inflammation by increasing the metabolism of tryptophan to kynurenine. This diversion of tryptophan metabolism negatively impacts serotonin synthesis and induces manifestations of anxiety and depression (Hillemacher et al., 2018).

### *Short-Chain Fatty Acids (SCFAs)*

Short-chain fatty acids (SCFAs) are neurohormonal signaling molecules with a relatively short carbon chain length, typically consisting of 1 to 6 carbon atoms (C1-6). SCFAs are primarily produced by gut microbiota through bacterial fermentation of dietary fibers and undigested starches. Gut microbiota break down complex carbohydrates into either of the three main SCFAs namely acetate (C2), propionate (C3), and butyrate (C4). Microbiota-generated SCFAs are absorbed into the bloodstream and circulated to different organ systems where they have various functional roles. SCFAs are known for their ability to interact with nerve cells by stimulating the sympathetic nervous system (Borre et al., 2014).

*Bacteroidetes*, *Firmicutes*, *Actinobacteria*, and *Proteobacteria* are the key microbial phyla that produce SCFAs in the gut. Acetate and propionate are predominantly produced by *Bacteroides* and *Bifidobacterium*, belonging to the *Bacteroidetes* and *Actinobacteria* phyla, respectively. *Clostridium*, *Ruminococcus*, and *Faecalibacterium*, belonging to the *Firmicutes* phylum, predominantly produce butyrate. *Proteobacteria* such as *Escherichia coli* also produce relatively minor quantities of SCFAs (Koh et al., 2016).

Butyrate plays a crucial role in maintaining the integrity of the gut barrier. Intestinal epithelial cells and microbes derive nutrients and energy from butyrate, and produce peptides that enforce integrity of the gut barrier. Depletion of butyrate-producing microbes causes the secreted mucus glycoproteins to act as alternate sources of energy, thereby eroding and compromising the intestinal barrier (Desai et al., 2016; Kelly et al., 2015). Compromised gut permeability allows inflammation-inducing bacterial lipopolysaccharides to enter the systemic circulation. Chronic low-grade inflammation percolates to compromised abilities of mood regulation and stress response (Taylor & Holscher, 2020b). Butyrate promotes differentiation and maturation of oligodendrocytes, which produce myelin, a fatty substance that forms a protective sheath around nerve fibers,

insulating and supporting neurons to facilitate efficient communication between nerve cells. The process of myelination is at its peak during adolescence (Spear, 2013), thereby emphasizing on the importance of SCFAs in neurodevelopment during adolescence. Butyrate also contributes significantly to the protection of dopaminergic neurons, and depletion of butyrate-producing microbes resulting in reduced SCFA levels has been associated with neurodegenerative diseases such as Parkinson's disease (Unger et al., 2016). Considering the crucial role of the neurotransmitter dopamine in mood regulation, factors that are deleterious to the dopaminergic system have a high potential to compromise mood regulating and stress response abilities (Yahfoufi et al., 2020b). Notably, reconstruction of the gut microbiota by FMT, a medical procedure involving the transfer of appropriately screened fecal material from a healthy donor into the gastrointestinal tract of a recipient via colonoscopy, nasogastric tube, or capsules with the goal to restore a healthy balance of gut microbiota, alleviated the symptoms associated with Parkinson's disease (H. Huang et al., 2019). This also highlights the potential to consider FMT as alternate therapeutic measures in refractory cases of anxiety and stress disorders, especially among adolescents.

The intestinal and the blood-brain barriers (BBB) share certain structural similarities including the tight junction proteins such as claudins, tricellulins, and occludins. *In vivo* evidence suggests that FMT-induced gut monocolonization of germ-free adult mice with SCFA-generating strains positively impacted BBB permeability and increased occludin expression levels (Braniste et al., 2014). SCFA supplementation has demonstrated restoration and normalization of microglial density and features, and has indicated the possibility of reversing microglial defects (Erny et al., 2015). Monocarboxylate transporters, expressed at the BBB, facilitate the translocation of SCFAs from the intestinal mucosa into the systemic circulation (Vijay & Morris, 2014), where they influence immune regulation and CNS function (De Vadder et al., 2014; Kelly et al., 2015). SCFAs are also known to modulate the synthesis of certain neurotransmitters such as serotonin and the expression of certain neurotransmitter receptors such as GABA receptors. SCFAs, particularly propionate has demonstrated the ability to modulate serotonergic signaling and increase serotonin secretion through their action on intestinal cells (Fukumoto et al., 2003; Reigstad et al., 2015). Regulation of gut-generated SCFAs is crucial because the intestinal cells are the primary source of serotonin secretion. SCFAs also play a central role in controlling several dopamine biosynthesis, degradation, and transport genes (DeCastro et al., 2005).

### *Vit K and Vit B Complex*

Vitamin K and vitamin B are groups of fat-soluble and water-soluble vitamins, respectively. While the vitamin K group is essential for blood clotting and bone health, vitamins of the B complex group play crucial roles in energy production, nerve function, and DNA synthesis. Certain species of the gut microbiota such as *Bifidobacterium*, *Clostridium*, *Bacteroides*, *Eubacterium*, *Escherichia*, *Enterococcus*, *Streptococcus*, and *Klebsiella* produce vitamin K2, the most active form of vitamin K, and some B vitamins, including folate, biotin, and vitamin B12 (Bailey et al., 2011; Gu & Li, 2016; O'Hara & Shanahan, 2006).

Folate, vitamin B12, and vitamin K2 are involved in the production of neurotransmitters such as serotonin, dopamine, and GABA. These neurotransmitters play a crucial role in mood regulation and thereby highlight the potential role of the vitamins B and K in alleviation of anxiety and stress in adolescents (Kennedy, 2016; Rudzki et al., 2021; Valizadeh & Valizadeh, 2011).

### *Glutamate*

Glutamate is an amino acid primarily synthesized by the neurons, and is one of the most abundant neurotransmitters in the CNS responsible for transmitting signals between neurons. Therefore, it plays a crucial role in various cognitive functions such as learning, memory, and information processing. Activation of the glutamate receptors present on the surface of neurons leads to the influx of calcium ions into the neurons, triggering a series of biochemical processes that facilitate neuronal communication.

Gut microbiota including certain strains of *Bifidobacterium*, *Lactobacillus*, and *Enterococcus* can metabolize dietary amino acids, such as glutamine, which serve as precursors for glutamate synthesis in the CNS. SCFAs and certain neurotransmitter precursors produced by gut microbiota can indirectly influence glutamate metabolism and neurotransmission, thereby affecting glutamate levels and signaling in the brain. SCFAs such as butyrate have been shown to modulate glutamate receptors and neurotransmitter release in the CNS, thereby impacting glutamate-mediated neuronal excitability and synaptic plasticity. Glutamate also impacts the gut-brain axis, and is involved in regulating gut motility, intestinal barrier function, and the modulation of gut microbiota (Janik et al., 2016).

While glutamate is essential for normal brain function, dysregulation of glutamate signaling has been implicated in the development and manifestation of certain disorders. Excessive glutamate signaling, particularly through the activation of N-methyl-D-aspartate (NMDA) receptors, has been associated with increased anxiety and stress responses. Overstimulation of NMDA receptors can lead to excitotoxicity, causing damage to neurons and impairing normal synaptic transmission. This excessive glutamate activity has been observed in various brain regions implicated in anxiety and stress regulation, such as the amygdala, prefrontal cortex, and hippocampus. Alterations in glutamate receptors and their associated signaling pathways can affect neuronal excitability and synaptic plasticity important for the regulation of anxiety-related behavior, and have been implicated in anxiety and stress disorders. Moreover, disruption of the balance between glutamate and GABA has been linked to anxiety and stress disorders. An imbalance leading to excessive glutamate activity or reduced GABAergic inhibition can disrupt the normal functioning of brain circuits involved in emotional regulation and contribute to the development of anxiety and stress symptoms (Cortese & Phan, 2005; Nasir et al., 2020; Sears & Hewett, 2021). Therefore, glutamate as a major excitatory neurotransmitter in the brain, may play a complex role in anxiety and stress disorders in adolescents.

### *Vitamin D*

Vitamin D is a fat-soluble vitamin that regulates the calcium and phosphate levels in the body by absorbing them from the diet. This ensures bone mineralization and growth, thereby being crucial to the maintenance of healthy bones and teeth. Vitamin D is synthesized by the skin through exposure to sunlight and can also be obtained through certain foods such as fatty fish, fortified dairy products, and egg yolks. Overconsumption of vitamin D, especially in the form of supplements, can result in toxicity because it is a fat-soluble vitamin.

Vitamin D obtained through sunlight exposure or dietary sources undergoes hydroxylation reactions in the liver and kidneys, and is converted into its active form, calcitriol. Gut microbiota, specifically the genera *Bacteroides* and *Bifidobacterium*, produce the CYP27A1 and CYP27B1 enzymes involved in these hydroxylation reactions, thereby influencing the metabolism of vitamin D. Therefore, gut microbiota can indirectly affect vitamin D levels by influencing the absorption and utilization of dietary vitamin D. A healthy gut microbiota composition has been shown to enhance the absorption of dietary vitamin D and contribute to its bioavailability (Yamamoto & Jørgensen, 2020).

Vitamin D receptors are present in several organ systems, thereby allowing it to influence several physiological functions including immune system modulation, muscle function, cell growth, regulation of gene expression, neurotransmitter function, inflammation, oxidative stress, and neuroplasticity. Dysregulation of any of these functions is implicated in psychiatric disorders. In the brain, vitamin D receptors are present in regions involved in mood regulation and stress response. This allows vitamin D to interact with and modulate the production and release of neurotransmitters such as serotonin, which are involved in regulation of mood, emotions, and stress responses. This is indicative of the potential involvement of vitamin D in anxiety and stress disorders (Milaneschi et al., 2014).

Research suggests that low vitamin D levels may be associated with increased risk and severity of anxiety and stress disorders in adolescents (Tarikere Satyanarayana et al., 2023). Furthermore, vitamin D supplementation has been shown to ameliorate symptoms of anxiety, suggesting its potential therapeutic role (Milaneschi et al., 2014).

### *Phosphophenolpyruvate*

Phosphoenolpyruvate (PEP) is an important intermediate molecule generated as a metabolite during the process of glycolysis, wherein energy is produced through the breakdown of glucose molecules. PEP plays a crucial role in cellular metabolism and in various biochemical pathways of the body as it serves as a precursor for the synthesis of various bioactive molecules, including amino acids, nucleotides, and certain neurotransmitters through the Shikimate pathway. Although PEP is not directly produced by gut microbiota, it plays a central role in the optimal functioning of the Shikimate pathway, which is predominantly facilitated by the gut microbiota. Aromatic amino acids such as phenylalanine, tyrosine, and tryptophan are synthesized in this pathway. These amino acids serve as building blocks for protein synthesis and are important for neurotransmitter production, immune regulation, and gut barrier function.

In the gut, PEP is formed as a breakdown product of fructose present in wheat. Some commonly used herbicides with antibiotic properties contain a substance called glyphosate. The antibiotic effect of glyphosate is implicated in the elimination of beneficial gut microbes, particularly *Bifidobacterium*, which is essential for the breakdown of wheat in the gut. It also depletes methionine that is required for DNA methylation and neurotransmitter production. Additionally, glyphosate acts as a chelating agent, reducing mineral levels, and downregulating the utilization of vitamin D. Recent research indicates a potential connection between the glyphosate-containing herbicide and compromised gut barrier function (D'Brant, 2014). This implies that a lack of PEP may impact neurotransmitter production and thereby potentially affect mood regulation and stress responses.

### *Omega-3 Polyunsaturated Fatty Acids*

Omega-3 polyunsaturated fatty acids (n-3 PUFAs) are essential fatty acids that play important roles in various physiological processes, including brain development and function, cardiovascular health, inflammation regulation, and immune system support. Alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) are the three main types of omega-3 fatty acids. Our body does not produce these essential fatty acids, and therefore, they must be obtained through dietary sources such as plant-based oils and fatty fishes. n-3 PUFA deficiency has been implicated in psychiatric disorders including schizophrenia, depression, and autism. Evidence also implicates adolescence as the most vulnerable period for the onset of majority of these psychiatric illnesses (Bondi et al., 2014; Kiecolt-Glaser et al., 2011).

Although omega-3 fatty acids are not derived from the microbiota, the interplay of n-3 PUFAs and the gut microbiota is evident from findings that show the association of omega-3 PUFA supplementation with decreased populations of *Faecalibacterium*, concomitant with an increased population of *Bacteroidetes* and *Lachnospiraceae* bacteria. The decrease in *Faecalibacterium* is intriguing because of its butyrate-producing role in the gut. However, the concomitant increase in *Bacteroidetes* and *Lachnospiraceae*, also butyrate-producing bacteria, ensures the balance in butyrate production. The contraindication of this finding highlights the involvement of host-specific factors including dietary and lifestyle choices in responses to omega-3 PUFA supplementation (Costantini et al., 2017).

Omega-6 fatty acids are also essential polyunsaturated fatty acids (n-6 PUFAs) found in vegetable oils and processed foods. However, over consumption of n-6 PUFAs contradict the benefits of n-3 PUFAs. A skewed n-3 to n-6 PUFA ratio resulting from dietary preferences leaning towards processed foods has been implicated in dopamine-related neurotransmission defects (Simopoulos, 2002). Dietary n-3 PUFA deficiency results in a compensatory increase of n-6 PUFAs as indicated by the replacement of DHA with docosapentaenoic acid (DPAn-6), an intermediate between EPA and DHA in the biosynthesis of omega-3 fatty acids, in an

investigation of the effects of PUFA-deficient diet in adolescent rats. The results were indicative of increased dopamine synthesis and altered expression of proteins required for dopamine-dependent neurotransmission (Bondi et al., 2014).

### *Polyphenols*

Polyphenols are a diverse group of plant-derived compounds that have been shown to have a variety of health benefits. Polyphenols are known to promote the growth of beneficial bacteria, inhibit the growth of pathogenic bacteria, modulate the production of short-chain fatty acids (SCFAs), and alter the gut barrier function. Flavonoids, resveratrol, epigallocatechin gallate (EGCG), and ellagitannins found in dietary sources including fruits, vegetables, nuts, and tea have been noted to have potential benefits in alleviating anxiety disorders (Cardona et al., 2013; Wang et al., 2022). Studies have indicated the benefits of polyphenol-rich diets containing urolithins and flavonoids in amelioration of anxiety and stress, especially among adolescents (Fisk et al., 2020).

### *Glycine*

Glycine is the simplest and smallest of the 20 amino acids commonly found in biological proteins and is a precursor for the synthesis of biologically important proteins including heme, creatine, and nucleotides. Additionally, glycine is involved in the regulation of various metabolic pathways, and has anti-inflammatory and antioxidant properties.

Glycine also acts as an inhibitory neurotransmitter in the CNS, and regulates neuronal excitability and modulates synaptic transmission.

While glycine is naturally produced in the body, it can also be obtained through dietary sources such as meat, fish, dairy products, and legumes. Certain species of gut microbiota such as *Lactobacillus* and *Bifidobacterium* breakdown certain compounds present in these dietary sources into metabolites, including glycine (Janik et al., 2016).

Glycine has been implicated in the regulation of anxiety and stress responses in adolescents. Studies suggest that glycine may exert anti-anxiety effects by interacting with specific receptors in the brain, such as the glycine receptors and NMDA receptors (Wolosker & Balu, 2020). Activation of glycine receptors can enhance inhibitory neurotransmission, reducing neuronal excitability and promoting a calming effect. Furthermore, glycine modulates the activity of the HPA axis and attenuates the release of stress-related hormones, such as cortisol, potentially reducing the physiological and psychological impact of anxiety and stress. Additionally, the potential ability of glycine to enhance sleep quality also emphasizes its role in regulating mood and stress responses (Bannai & Kawai, 2012; Inagawa et al., 2006).

## Management of Treatment-Resistant Anxiety Disorders: Current and Novel Therapeutic Strategies

Treatment and management of stress and anxiety disorders, especially in the adolescent age group does not follow the ‘one size fits all’ principle. While recent advances have ushered in many effective therapeutic approaches, refractory or treatment-resistant cases do not yield satisfactory results in response to the standard interventions. The existing management and treatment strategies can be broadly categorized into pharmacological approaches, novel pharmacotherapeutic agents, and transdiagnostic interventions.

## Pharmacological Approaches

The existing interventions involving pharmacological approaches encompass a range of medications such as selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), azapirones, antipsychotics, antihistamines, alpha-and beta-adrenergic medications, and GABAergic medications.

### *Serotonergic Agents*

Selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) are both antidepressant medications that work facilitate mood regulation and reduction of anxiety symptoms. SSRIs block the reuptake of serotonin and increase its levels in the brain. Similarly, SNRIs increase the levels of both serotonin and norepinephrine in the brain. While SSRIs are commonly used to treat various anxiety disorders, including panic disorder, generalized anxiety disorder (GAD), social anxiety disorder (SAD), and specific phobias, SNRIs can be effective in managing symptoms of depression and anxiety, simultaneously.

Both, SSRIs and SNRIs are commonly prescribed and are effective in treating anxiety disorders in adolescents. However, some side effects to consider include potential gastrointestinal issues, headaches, and changes in blood pressure or heart rate. An initial worsening of anxiety symptoms before improvement occurs is also seen in some cases. Notably, the risk of suicidal ideation when starting or discontinuing these medications warrants close monitoring and poses a high level of threat considering that the high rate of patient non-compliance and non-adherence to treatment among adolescents (Giovanni B. Cassano, 2022; Lagerberg et al., 2022).

### *GABAergic medications*

GABAergic medications, including benzodiazepines, pregabalin, and gabapentin, primarily target the GABA neurotransmitter system that helps to reduce brain activity. These medications enhance the effect of GABA, leading to an overall reduction in neuronal activity resulting in a calming or sedative effect. While benzodiazepines can be effective for short-term relief of severe anxiety symptoms, they have a high risk of dependence and withdrawal, especially in adolescents. Although pregabalin and gabapentin have a lower risk of dependence, side effects like dizziness and sedation may be seen in some cases (Nasir et al., 2020).

### *Azapirones*

Azapirones are medications that exert an anxiolytic effect by reducing anxiety, especially in cases of generalized anxiety disorder. They act on the serotonin and dopamine receptors in the brain, and alleviate anxiety symptoms without having sedation effects, withdrawal symptoms, or risk of dependence. However, they may take several weeks to show their full effect, and some cases may not experience significant relief of symptoms, especially among adolescents owing to challenges such as non-adherence to the medication regimen (Chessick et al., 2006).

### *Antipsychotics*

Antipsychotics are generally not considered first-line treatments for anxiety disorders in adolescents, and are primarily used to treat psychotic disorders such as schizophrenia. Their mechanism of action involves the modulation of various neurotransmitters in the brain. While some atypical antipsychotics may be used off-label in extreme and refractory cases of anxiety disorders, they can have significant side effects including weight gain, metabolic changes, and movement disorders (Garakani et al., 2022; Hershenberg et al., 2014).

### *Antihistamines*

Antihistamines reduce anxiety and have a calming effect. Although these medications are not typically used as a first-line treatment for chronic anxiety disorders, they may be prescribed to manage acute anxiety in certain

situations such as before medical procedures or for short-term relief of acute anxiety. However, they have sedative effects and can cause drowsiness, which may interfere with academic performance and daily activities among adolescents (Garakani et al., 2020b; Ozdemir et al., 2014).

### *Alpha- and Beta-Adrenergic Medications*

Alpha- and beta-adrenergic medications target the adrenergic system, which regulates the release of norepinephrine and epinephrine, hormones involved in stress regulation and management of the 'fight or flight' responses of the body. These medications can be helpful in managing physical manifestations of anxiety, such as rapid heart rate and trembling, and are particularly helpful in situations where anxiety symptoms are acute, such as before public speaking. However, they do not directly address the underlying psychological aspects of anxiety and are known to have some side effects including fatigue, dizziness, and changes in blood pressure (Garakani et al., 2020b; Stemmelin et al., 2008).

## Novel Pharmacotherapeutic Agents

Considering the challenges associated with certain patient groups such as adolescents and treatment-resistant cases of anxiety and stress disorders, research has recently focused on some novel treatment and management strategies that combine both medicines and a deeper psychological understanding of the patient and their specific disorder. This ensures a more tailored treatment approach, customized to the specific needs of the patient, and has the potential to address issues related to non-compliant patient groups and treatment-resistant cases. These novel pharmacotherapeutic agents, including glutamate modulators, neuropeptides, neurosteroids, cannabinoids, and natural remedies, exert their effects by targeting and interacting with various neurotransmitters and pathways.

### *Glutamate Modulators*

Glutamate modulators target the glutamate system, which is the primary excitatory neurotransmitter in the brain. They differ from the GABAergic medications in their mode of action. These medications aim to modulate glutamate activity and signaling, and thereby exert calming effects in the brain. Therefore, these modulators are being explored for their potential in treating anxiety disorders, particularly in GAD or SAD. While withdrawal and dependence related side effects are lower with glutamate modulators, adverse reactions such as dissociative and hallucinogenic effects may occur. Therefore, although glutamate modulators are a promising option for refractory cases, further research and caution in clinical use is recommended (Nasir et al., 2020).

### *Neuropeptides*

Neuropeptides are small protein molecules in the body that play various roles in functions of the CNS including communication. Some neuropeptides, such as oxytocin, often referred to as the 'love hormone', has shown promise in promoting social bonding and reducing social anxiety in certain individuals. However, research on neuropeptide-based treatments is still in its early stages, and more evidence is needed to support their use in adolescents (Kupcova et al., 2022).

### *Neurosteroids*

Neurosteroids are naturally occurring steroids that affect brain function. Some neurosteroids such as PH94B, an inhaled neurosteroid, has shown promise in reducing social anxiety symptoms. However, further research is needed to establish its safety and effectiveness (Longone et al., 2011).

### *Cannabinoids*

Cannabinoids, derived from the cannabis plant, have been explored for their potential therapeutic effects on anxiety disorders. Cannabidiol (CBD), in particular, has been studied for its anxiolytic properties. However, the research on cannabinoids and anxiety in adolescents is still limited, and there are concerns about potential adverse effects and long-term safety (Tambaro & Bortolato, n.d.).

### *Natural Remedies*

Natural remedies encompass various herbal supplements and alternative therapies that may be used to manage anxiety. Examples include certain herbal teas and aromatherapy using certain essential oils. While some of these remedies have some calming effects, their efficacy in non-compliant adolescents and refractory cases is debatable. The safety related to the consumption and inhalation of these remedies and their effects on various organ systems also raises several questions.

## Transdiagnostic Interventions

Transdiagnostic interventions refer to therapeutic approaches that are designed to target and treat underlying processes or mechanisms that are common across multiple psychological disorders, rather than focusing on specific symptoms or diagnoses. These interventions aim to address shared features or core mechanisms that contribute to various mental health conditions, thereby offering a more efficient and flexible treatment approach (Akbari et al., 2015; Cuijpers et al., 2023).

### *Cognitive Behavioral Therapy (CBT)*

Cognitive behavioral therapy (CBT) is one of the most widely used and researched transdiagnostic interventions. It is based on the understanding that thoughts, emotions, and behaviors are interconnected, and can influence each other. CBT helps individuals identify, challenge, and replace negative thought patterns and behaviors that contribute to their emotional distress and psychological symptoms with more balanced and adaptive thoughts.

Different stress and anxiety disorders often present with similar manifestations, which can be addressed more efficiently with a more unified and efficient treatment approach rather than treating every symptom separately.

CBT typically requires the therapist and the individual to work together, and this ensures personalized and flexible treatments that target the shared underlying factors in various anxiety disorders. CBT is known for its evidence-based effectiveness in treating a wide range of mental health conditions, including anxiety disorders.

However, patient non-compliance and avoidance behavior that is commonly seen among adolescents drastically affects the success rates of CBT (Norton & Barrera, 2012; Schaeuffele et al., 2021).

## Fecal Microbiota Transplantation (FMT)

FMT, a medical procedure involving the transfer of fecal material from a healthy donor to the gastrointestinal tract of a recipient has been the focus of research for several treatment-resistant diseases for over a decade now. The goal of FMT is to restore the balance of gut microbiota and treat various medical conditions associated with dysbiosis. The procedure is primarily used to manage refractory cases of recurrent *Clostridioides difficile* infection (CDI), a severe and persistent gastrointestinal infection (Gupta et al., 2016; Halaweish et al., 2022; Hao et al., 2023; Kassam et al., 2013).

The primary purpose of FMT is to restore the balance of gut microbiota in the recipient, especially in cases of dysbiosis or microbial imbalances. FMT works by introducing a diverse and healthy microbiota into the recipient gut, which helps to combat the harmful bacteria causing the infection.

The success of FMT may vary depending on several factors, including the diversity and specific composition of the gut microbiome, the immune system, host genetics, and working protocols (fecal amount, number of infusions, route of delivery, and adjuvant treatments). Additionally, the extent to which the transplanted microbial population from the donor becomes integrated and functional within the gut of the recipient may be related to the clinical success of FMT (Porcari et al., 2023).

The procedure is considered safe and effective for CDI, and has recently been approved for clinical use in human refractory cases of rCDI. Research is also ongoing to explore its potential benefits in other conditions, such as inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), metabolic disorders, and even certain neurological and psychiatric disorders (Cai et al., 2022; Chinna Meyyappan et al., 2020; Doll et al., 2022; Hao et al., 2023; H. Huang et al., 2019; Ser et al., 2021; Settanni et al., 2021).

## Conclusion

In this comprehensive review, we highlight the critical role of the gut microbiota and its associated metabolites in influencing stress and anxiety disorders, particularly during the vulnerable phase of adolescence. Dysbiosis in the gut microbiota can have profound effects on the nervous, immune, and endocrine systems, contributing to the manifestation of psychiatric disorders in adolescents. The bidirectional communication pathway known as the microbiota-gut-brain axis plays a pivotal role in this complex interplay.

While conventional therapeutic measures exist for stress and anxiety disorders, they may not always address the specific needs of adolescents. Gut-microbiota-based therapeutic approaches offer a promising avenue for tailored treatments, taking into account the unique gut microbiota compositions among patient groups. However, challenges such as prolonged adherence and dietary preferences need to be overcome for the success of these approaches in adolescents.

We present an in-depth analysis of microbiota-associated metabolites that have shown potential in alleviating stress and anxiety symptoms. Understanding the roles of these metabolites is crucial in developing targeted and effective treatments for psychiatric disorders. Moreover, the findings from this review could benefit unconventional treatment strategies, such as FMT, which are being explored as promising alternatives for psychiatric disorder management.

In summary, this review underscores the importance of considering the gut-brain axis and the influence of gut microbiota in developing novel therapeutic interventions for stress and anxiety disorders in adolescents. This study contributes to advancing personalized and effective treatments for the challenging and complex landscape of adolescent mental health, shedding light on the role of microbiota-associated metabolites and their potential benefits. Future research in the pursuit of optimal mental well-being in this critical phase of human life that bridges the gap between childhood and adulthood would benefit from this direction and potentially transform the management of stress and anxiety disorders in adolescents.

## Limitations

Although this review offers valuable insights into the role of gut microbiota and its associated metabolites in stress and anxiety disorders during adolescence, it is important to acknowledge certain limitations.

We focus primarily on the effects of dysbiosis on the nervous, immune, and endocrine systems, with special emphasis on their roles during adolescence. While this emphasis is appropriate given the context of the

review, it may result in overlooking other potential internal and environmental factors or systems that contribute to the pathologies of stress and anxiety disorders during this critical phase of life.

Adolescence encompasses a wide age range (10 to 19 years), during which individuals undergo significant physical and psychological changes. However, the review may not thoroughly explore how these variations in age, hormonal changes, and developmental stages can influence the gut microbiota composition and its impact on stress and anxiety disorders.

While a summary of the existing therapeutic approaches has been mentioned in the review, it is by no means an exhaustive list. It is also essential to note that the majority of the evidence presented may come from preclinical studies or observational studies. The lack of robust clinical trials that specifically target stress and anxiety disorders in adolescents using microbiota-based interventions limits the conclusive evidence regarding the effectiveness of such approaches.

The review suggests that gut-microbiota-based therapeutic approaches have the potential to be tailor-made for certain patient groups, including adolescents with shared commonalities. However, it is essential to consider the variability of gut microbiota composition among individuals, even within the same age group, ethnicity, or community. The extent to which the findings can be generalized to all adolescents with stress and anxiety disorders requires further investigation.

While the review discusses the potential of gut microbiota-associated metabolites as promising treatment options, it does not extensively delve into their long-term efficacy and safety. Long-term studies on the stability of gut microbiota alterations, the durability of treatment effects, and potential adverse effects are critical in evaluating the feasibility of these interventions.

While we believe that unconventional alternatives like FMT as a therapeutic approach for refractory cases of psychiatric disorders will benefit from the findings of this review, it is essential to address the ethical implications and potential risks associated with such treatments, especially in the context of treating vulnerable populations like adolescents.

In conclusion, while the review provides a comprehensive overview of the current understanding of the role of gut microbiota in stress and anxiety disorders during adolescence, its limitations must be taken into account. Addressing these limitations through further research and clinical trials will strengthen the evidence base and facilitate the development of targeted and effective therapeutic strategies for improving the mental well-being of adolescents facing stress and anxiety disorders.

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## References

Akbari, M., Roshan, R., Shabani, A., Fata, L., Reza Shairi, M., & Zarghami, F. (2015). Transdiagnostic Treatment of Co-occurrence of Anxiety and Depressive Disorders based on Repetitive Negative Thinking: A Case Series. In *Iranian J Psychiatry* (Vol. 10).

Al-Harbi, K. S. (2012). Treatment-resistant depression: Therapeutic trends, challenges, and future directions. In *Patient Preference and Adherence* (Vol. 6, pp. 369–388). https://doi.org/10.2147/PPA.S29716

Ansara, E. D. (2020). Management of treatment-resistant generalized anxiety disorder. *Mental Health Clinician*, *10*(6), 326–334. https://doi.org/10.9740/mhc.2020.11.326

Bailey, M. T., Dowd, S. E., Galley, J. D., Hufnagle, A. R., Allen, R. G., & Lyte, M. (2011). Exposure to a social stressor alters the structure of the intestinal microbiota: Implications for stressor-induced immunomodulation. *Brain, Behavior, and Immunity*, *25*(3), 397–407. https://doi.org/10.1016/j.bbi.2010.10.023

Balan, Y., Gaur, A., Sakthivadivel, V., Kamble, B., & Sundaramurthy, R. (2021). Is the Gut Microbiota a Neglected Aspect of Gut and Brain Disorders? *Cureus*. https://doi.org/10.7759/cureus.19740

Bannai, M., & Kawai, N. (2012). New therapeutic strategy for amino acid medicine: Glycine improves the quality of sleep. In *Journal of Pharmacological Sciences* (Vol. 118, Issue 2, pp. 145–148). Japanese Pharmacological Society. https://doi.org/10.1254/jphs.11R04FM

Barnea-Goraly, N., Menon, V., Eckert, M., Tamm, L., Bammer, R., Karchemskiy, A., Dant, C. C., & Reiss, A. L. (2005). White matter development during childhood and adolescence: A cross-sectional diffusion tensor imaging study. *Cerebral Cortex*, *15*(12), 1848–1854. https://doi.org/10.1093/cercor/bhi062

Barrett, E., Ross, R. P., O'Toole, P. W., Fitzgerald, G. F., & Stanton, C. (2012). γ-Aminobutyric acid production by culturable bacteria from the human intestine. *Journal of Applied Microbiology*, *113*(2), 411–417. https://doi.org/10.1111/j.1365-2672.2012.05344.x

Benes, F. M. (1989). *Myelination of Cortical-Hippocampal Relays During Late Adolescence 585* (Vol. 15, Issue 4). https://academic.oup.com/schizophreniabulletin/article/15/4/585/1924501

Bibbò, S., Fusco, S., Ianiro, G., Settanni, C. R., Ferrarese, D., Grassi, C., Cammarota, G., & Gasbarrini, A. (2022). Gut microbiota in anxiety and depression: Pathogenesis and therapeutics. *Frontiers in Gastroenterology*, *1*. https://doi.org/10.3389/fgstr.2022.1019578

Blakemore, S. J., & Choudhury, S. (2006). Development of the adolescent brain: Implications for executive function and social cognition. In *Journal of Child Psychology and Psychiatry and Allied Disciplines* (Vol. 47, Issues 3–4, pp. 296–312). https://doi.org/10.1111/j.1469-7610.2006.01611.x

Bokma, W. A., Wetzer, G. A. A. M., Gehrels, J. B., Penninx, B. W. J. H., Batelaan, N. M., & van Balkom, A. L. J. M. (2019). Aligning the many definitions of treatment resistance in anxiety disorders: A systematic review. In *Depression and Anxiety* (Vol. 36, Issue 9, pp. 801–812). Blackwell Publishing Inc. https://doi.org/10.1002/da.22895

Bondi, C. O., Taha, A. Y., Tock, J. L., Totah, N. K. B., Cheon, Y., Torres, G. E., Rapoport, S. I., & Moghaddam, B. (2014). Adolescent behavior and dopamine availability are uniquely sensitive to dietary omega-3 fatty acid deficiency. *Biological Psychiatry*, *75*(1), 38–46. https://doi.org/10.1016/j.biopsych.2013.06.007

Borre, Y. E., O'Keeffe, G. W., Clarke, G., Stanton, C., Dinan, T. G., & Cryan, J. F. (2014). Microbiota and neurodevelopmental windows: implications for brain disorders. In *Trends in molecular medicine* (Vol. 20, Issue 9, pp. 509–518). https://doi.org/10.1016/j.molmed.2014.05.002

Braniste, V., Al-Asmakh, M., Kowal, C., Anuar, F., Abbaspour, A., Tóth, M., Korecka, A., Bakocevic, N., Guan, N. L., Kundu, P., Gulyás, B., Halldin, C., Hultenby, K., Nilsson, H., Hebert, H., Volpe, B. T., Diamond, B., & Pettersson, S. (2014). The gut microbiota influences blood-brain barrier permeability in mice. *Science Translational Medicine*, *6*(263). https://doi.org/10.1126/scitranslmed.3009759

Bravo, J. A., Forsythe, P., Chew, M. V., Escaravage, E., Savignac, H. M., Dinan, T. G., Bienenstock, J., & Cryan, J. F. (2011). Ingestion of Lactobacillus strain regulates emotional behavior and central GABA receptor expression in a mouse via the vagus nerve. *Proceedings of the National Academy of Sciences of the United States of America*, *108*(38), 16050–16055. https://doi.org/10.1073/pnas.1102999108

Brizio, A., Gabbatore, I., Tirassa, M., & Bosco, F. M. (2015). "No more a child, not yet an adult": Studying social cognition in adolescence. *Frontiers in Psychology*, *6*(AUG). https://doi.org/10.3389/fpsyg.2015.01011

Cai, T., Zheng, S. P., Shi, X., Yuan, L. Z., Hu, H., Zhou, B., Xiao, S. L., & Wang, F. (2022). Therapeutic effect of fecal microbiota transplantation on chronic unpredictable mild stress-induced depression. *Frontiers in Cellular and Infection Microbiology*, *12*. https://doi.org/10.3389/fcimb.2022.900652

Cardona, F., Andrés-Lacueva, C., Tulipani, S., Tinahones, F. J., & Queipo-Ortuño, M. I. (2013). Benefits of polyphenols on gut microbiota and implications in human health. In *Journal of Nutritional Biochemistry* (Vol. 24, Issue 8, pp. 1415–1422). https://doi.org/10.1016/j.jnutbio.2013.05.001

Chen, Y., Xu, J., & Chen, Y. (2021a). Regulation of neurotransmitters by the gut microbiota and effects on cognition in neurological disorders. In *Nutrients* (Vol. 13, Issue 6). MDPI. https://doi.org/10.3390/nu13062099

Chen, Y., Xu, J., & Chen, Y. (2021b). Regulation of neurotransmitters by the gut microbiota and effects on cognition in neurological disorders. In *Nutrients* (Vol. 13, Issue 6). MDPI. https://doi.org/10.3390/nu13062099

Chessick, C. A., Allen, M. H., Thase, M. E., Batista Miralha da Cunha, A. A. B. C., Kapczinski, F., Silva de Lima, M., & dos Santos Souza, J. J. S. S. (2006). Azapirones for generalized anxiety disorder. In *Cochrane Database of Systematic Reviews* (Vol. 2006, Issue 3). John Wiley and Sons Ltd. https://doi.org/10.1002/14651858.CD006115

Chinna Meyyappan, A., Forth, E., Wallace, C. J. K., & Milev, R. (2020). Effect of fecal microbiota transplant on symptoms of psychiatric disorders: A systematic review. *BMC Psychiatry*, *20*(1). https://doi.org/10.1186/s12888-020-02654-5

Chiu, A., Falk, A., & Walkup, J. T. (2016). Anxiety Disorders Among Children and Adolescents. *FOCUS*, *14*(1), 26–33. https://doi.org/10.1176/appi.focus.20150029

Choi, T. Y., Choi, Y. P., & Koo, J. W. (2020). Mental disorders linked to crosstalk between the gut microbiome and the brain. In *Experimental Neurobiology* (Vol. 29, Issue 6, pp. 403–416). Korean Society for Neurodegenerative Disease. https://doi.org/10.5607/EN20047

Chubar, V., Van Leeuwen, K., Bijttebier, P., Van Assche, E., Bosmans, G., Van den Noortgate, W., van Winkel, R., Goossens, L., & Claes, S. (2020). Gene–environment interaction: New insights into perceived parenting and social anxiety among adolescents. *European Psychiatry*, *63*(1). https://doi.org/10.1192/j.eurpsy.2020.62

Clapp, M., Aurora, N., Herrera, L., Bhatia, M., Wilen, E., & Wakefield, S. (2017a). Gut Microbiota's Effect on Mental Health: The Gut-Brain Axis. *Clinics and Practice*, *7*(4), 987. https://doi.org/10.4081/cp.2017.987

Clapp, M., Aurora, N., Herrera, L., Bhatia, M., Wilen, E., & Wakefield, S. (2017b). Gut Microbiota's Effect on Mental Health: The Gut-Brain Axis. *Clinics and Practice*, *7*(4), 987. https://doi.org/10.4081/cp.2017.987

Cohen Kadosh, K., Basso, M., Knytl, P., Johnstone, N., Lau, J. Y. F., & Gibson, G. R. (2021). Psychobiotic interventions for anxiety in young people: a systematic review and meta-analysis, with youth consultation. *Translational Psychiatry*, *11*(1). https://doi.org/10.1038/s41398-021-01422-7

Cortese, B. M., & Phan, K. L. (2005). The role of glutamate in anxiety and related disorders. In *CNS Spectrums* (Vol. 10, Issue 10, pp. 820–830). Cambridge University Press. https://doi.org/10.1017/S1092852900010427

Costantini, L., Molinari, R., Farinon, B., & Merendino, N. (2017). Impact of omega-3 fatty acids on the gut microbiota. In *International Journal of Molecular Sciences* (Vol. 18, Issue 12). MDPI AG. https://doi.org/10.3390/ijms18122645

Crone, E. A., & Dahl, R. E. (2012). Understanding adolescence as a period of social-affective engagement and goal flexibility. *Nature Reviews Neuroscience*, *13*(9), 636–650. https://doi.org/10.1038/nrn3313

Cruz-Pereira, J. S., Rea, K., Nolan, Y. M., O'leary, O. F., Dinan, T. G., & Cryan, J. F. (2019). *Depression's Unholy Trinity: Dysregulated Stress, Immunity, and the Microbiome*. https://doi.org/10.1146/annurev-psych-122216

Cryan, J. F. (2016). Stress and the microbiota-gut-brain axis: An evolving concept in psychiatry. In *Canadian Journal of Psychiatry* (Vol. 61, Issue 4, pp. 201–203). SAGE Publications Inc. https://doi.org/10.1177/0706743716635538

Cryan, J. F., & Dinan, T. G. (2012). Mind-altering microorganisms: The impact of the gut microbiota on brain and behaviour. In *Nature Reviews Neuroscience* (Vol. 13, Issue 10, pp. 701–712). https://doi.org/10.1038/nrn3346

Cuijpers, P., Miguel, C., Ciharova, M., Ebert, D., Harrer, M., & Karyotaki, E. (2023). Transdiagnostic treatment of depression and anxiety: a meta-analysis. *Psychological Medicine*, 1–12. https://doi.org/10.1017/s0033291722003841

D'Brant, J. (2014). GMOs, Gut Flora, the Shikimate Pathway and Cytochrome Dysregulation. *Nutritional Perspectives: Journal of the Council on Nutrition*, *37*(1).

De Vadder, F., Kovatcheva-Datchary, P., Goncalves, D., Vinera, J., Zitoun, C., Duchampt, A., Bäckhed, F., & Mithieux, G. (2014). Microbiota-generated metabolites promote metabolic benefits via gut-brain neural circuits. *Cell*, *156*(1–2), 84–96. https://doi.org/10.1016/j.cell.2013.12.016

DeCastro, M., Nankova, B. B., Shah, P., Patel, P., Mally, P. V., Mishra, R., & La Gamma, E. F. (2005). Short chain fatty acids regulate tyrosine hydroxylase gene expression through a cAMP-dependent signaling pathway. *Molecular Brain Research*, *142*(1), 28–38. https://doi.org/10.1016/j.molbrainres.2005.09.002

Desai, M. S., Seekatz, A. M., Koropatkin, N. M., Kamada, N., Hickey, C. A., Wolter, M., Pudlo, N. A., Kitamoto, S., Terrapon, N., Muller, A., Young, V. B., Henrissat, B., Wilmes, P., Stappenbeck, T. S., Núñez, G., & Martens, E. C. (2016). A Dietary Fiber-Deprived Gut Microbiota Degrades the Colonic Mucus Barrier and Enhances Pathogen Susceptibility. *Cell*, *167*(5), 1339-1353.e21. https://doi.org/10.1016/j.cell.2016.10.043

Desbonnet, L., Clarke, G., Traplin, A., O'Sullivan, O., Crispie, F., Moloney, R. D., Cotter, P. D., Dinan, T. G., & Cryan, J. F. (2015). Gut microbiota depletion from early adolescence in mice: Implications for brain and behaviour. *Brain, Behavior, and Immunity*, *48*, 165–173. https://doi.org/10.1016/j.bbi.2015.04.004

Dinan, T. G., & Cryan, J. F. (2012). Regulation of the stress response by the gut microbiota: Implications for psychoneuroendocrinology. In *Psychoneuroendocrinology* (Vol. 37, Issue 9, pp. 1369–1378). https://doi.org/10.1016/j.psyneuen.2012.03.007

Dinan, T. G., & Cryan, J. F. (2013). Melancholic microbes: A link between gut microbiota and depression? In *Neurogastroenterology and Motility* (Vol. 25, Issue 9, pp. 713–719). https://doi.org/10.1111/nmo.12198

Doll, J. P. K., Vázquez-Castellanos, J. F., Schaub, A. C., Schweinfurth, N., Kettelhack, C., Schneider, E., Yamanbaeva, G., Mählmann, L., Brand, S., Beglinger, C., Borgwardt, S., Raes, J., Schmidt, A., & Lang, U. E. (2022). Fecal Microbiota Transplantation (FMT) as an Adjunctive Therapy for Depression—Case Report. *Frontiers in Psychiatry*, *13*. https://doi.org/10.3389/fpsyt.2022.815422

Du, Y., Gao, X. R., Peng, L., & Ge, J. F. (2020). Crosstalk between the microbiota-gut-brain axis and depression. In *Heliyon* (Vol. 6, Issue 6). Elsevier Ltd. https://doi.org/10.1016/j.heliyon.2020.e04097

Eiland, L., & Romeo, R. D. (2013). Stress and the developing adolescent brain. In *Neuroscience* (Vol. 249, pp. 162–171). https://doi.org/10.1016/j.neuroscience.2012.10.048

Erny, D., De Angelis, A. L. H., Jaitin, D., Wieghofer, P., Staszewski, O., David, E., Keren-Shaul, H., Mahlakoiv, T., Jakobshagen, K., Buch, T., Schwierzeck, V., Utermöhlen, O., Chun, E., Garrett, W. S., Mccoy, K. D., Diefenbach, A., Staeheli, P., Stecher, B., Amit, I., & Prinz, M. (2015). Host microbiota

constantly control maturation and function of microglia in the CNS. *Nature Neuroscience*, *18*(7), 965–977. https://doi.org/10.1038/nn.4030
Evrensel, A., Ünsalver, B. Ö., & Ceylan, M. E. (2020). Neuroinflammation, gut-brain axis and depression. In *Psychiatry Investigation* (Vol. 17, Issue 1, pp. 2–8). Korean Neuropsychiatric Association. https://doi.org/10.30773/pi.2019.08.09
Fan, Y., & Pedersen, O. (2021). Gut microbiota in human metabolic health and disease. In *Nature Reviews Microbiology* (Vol. 19, Issue 1, pp. 55–71). Nature Research. https://doi.org/10.1038/s41579-020-0433-9
Fisk, J., Khalid, S., Reynolds, S. A., & Williams, C. M. (2020). Effect of 4 weeks daily wild blueberry supplementation on symptoms of depression in adolescents. *British Journal of Nutrition*, *124*(2), 181–188. https://doi.org/10.1017/S0007114520000926
Flint, H. J., Scott, K. P., Louis, P., & Duncan, S. H. (2012). The role of the gut microbiota in nutrition and health. In *Nature Reviews Gastroenterology and Hepatology* (Vol. 9, Issue 10, pp. 577–589). https://doi.org/10.1038/nrgastro.2012.156
Foster, J. A., & McVey Neufeld, K. A. (2013). Gut-brain axis: How the microbiome influences anxiety and depression. In *Trends in Neurosciences* (Vol. 36, Issue 5, pp. 305–312). https://doi.org/10.1016/j.tins.2013.01.005
Foster, J. A., Rinaman, L., & Cryan, J. F. (2017a). Stress & the gut-brain axis: Regulation by the microbiome. In *Neurobiology of Stress* (Vol. 7, pp. 124–136). Elsevier Inc. https://doi.org/10.1016/j.ynstr.2017.03.001
Foster, J. A., Rinaman, L., & Cryan, J. F. (2017b). Stress & the gut-brain axis: Regulation by the microbiome. In *Neurobiology of Stress* (Vol. 7, pp. 124–136). Elsevier Inc. https://doi.org/10.1016/j.ynstr.2017.03.001
Frankiensztajn, L. M., Elliott, E., & Koren, O. (2020a). The microbiota and the hypothalamus-pituitary-adrenocortical (HPA) axis, implications for anxiety and stress disorders. In *Current Opinion in Neurobiology* (Vol. 62, pp. 76–82). Elsevier Ltd. https://doi.org/10.1016/j.conb.2019.12.003
Frankiensztajn, L. M., Elliott, E., & Koren, O. (2020b). The microbiota and the hypothalamus-pituitary-adrenocortical (HPA) axis, implications for anxiety and stress disorders. In *Current Opinion in Neurobiology* (Vol. 62, pp. 76–82). Elsevier Ltd. https://doi.org/10.1016/j.conb.2019.12.003
Freed, R. D., Mehra, L. M., Laor, D., Patel, M., Alonso, C. M., Kim-Schulze, S., & Gabbay, V. (2019). Anhedonia as a clinical correlate of inflammation in adolescents across psychiatric conditions. *World Journal of Biological Psychiatry*, *20*(9), 712–722. https://doi.org/10.1080/15622975.2018.1482000
Fröhlich, E., & Wahl, R. (2019). Microbiota and Thyroid Interaction in Health and Disease. In *Trends in Endocrinology and Metabolism* (Vol. 30, Issue 8, pp. 479–490). Elsevier Inc. https://doi.org/10.1016/j.tem.2019.05.008
Fukumoto, S., Tatewaki, M., Yamada, T., Fujimiya, M., Mantyh, C., Voss, M., Eubanks, S., Harris, M., Pappas, T. N., Takahashi, T., & Pap-pas, T. N. (2003). *Short-chain fatty acids stimulate colonic transit via intraluminal 5-HT release in rats*. https://doi.org/10.1152/ajpregu.00442.2002.-We
Garakani, A., Freire, R. C., Buono, F. D., Thom, R. P., Larkin, K., Funaro, M. C., Salehi, M., & Perez-Rodriguez, M. M. (2022). An umbrella review on the use of antipsychotics in anxiety disorders: A registered report protocol. *PLoS ONE*, *17*(6 June). https://doi.org/10.1371/journal.pone.0269772
Garakani, A., Murrough, J. W., Freire, R. C., Thom, R. P., Larkin, K., Buono, F. D., & Iosifescu, D. V. (2020a). Pharmacotherapy of Anxiety Disorders: Current and Emerging Treatment Options. In *Frontiers in Psychiatry* (Vol. 11). Frontiers Media S.A. https://doi.org/10.3389/fpsyt.2020.595584
Garakani, A., Murrough, J. W., Freire, R. C., Thom, R. P., Larkin, K., Buono, F. D., & Iosifescu, D. V. (2020b). Pharmacotherapy of Anxiety Disorders: Current and Emerging Treatment Options. In *Frontiers in Psychiatry* (Vol. 11). Frontiers Media S.A. https://doi.org/10.3389/fpsyt.2020.595584
Gardner, M., & Steinberg, L. (2005). Peer influence on risk taking, risk preference, and risky decision making in adolescence and adulthood: An experimental study. *Developmental Psychology*, *41*(4), 625–635. https://doi.org/10.1037/0012-1649.41.4.625

Giedd, J. N. (2009). Linking Adolescent Sleep, Brain Maturation, and Behavior. In *Journal of Adolescent Health* (Vol. 45, Issue 4, pp. 319–320). https://doi.org/10.1016/j.jadohealth.2009.07.007

Giedd, J. N., Blumenthal, J., Jeffries, N. O., Castellanos, F. X., Liu, H., Zijdenbos, A., Evans, A. C., & Rapoport, J. L. (1999). Brain development during childhood and adolescence: a longitudinal MRI study. In *J. Comput. Assist. Tomogr* (Vol. 51, Issue 2). Plenum. http://neurosci.nature.com

Giedd, J. N., Snell, J. W., Lange, N., Rajapakse, J. C., Casey, B. J., Kozuch, P. L., Vaituzis, A. C., Vauss, Y. C., Hamburger, S. D., Kaysen, D., & Rapoport, J. L. (n.d.). *Quantitative Magnetic Resonance Imaging of Human Brain Development: Ages 4-18*. https://academic.oup.com/cercor/article/6/4/551/309869

Giorgio, A., Watkins, K. E., Chadwick, M., James, S., Winmill, L., Douaud, G., De Stefano, N., Matthews, P. M., Smith, S. M., Johansen-Berg, H., & James, A. C. (2010). Longitudinal changes in grey and white matter during adolescence. *NeuroImage*, *49*(1), 94–103. https://doi.org/10.1016/j.neuroimage.2009.08.003

Giovanni B. Cassano, M. (2022). Psychopharmacology of anxiety disorders. *Dialogues Clin Neurosci*, *4*(3), 271–285. https://doi.org/doi: 10.31887/DCNS.2002.4.3/gcassano

Goddings, A. L., Mills, K. L., Clasen, L. S., Giedd, J. N., Viner, R. M., & Blakemore, S. J. (2014). The influence of puberty on subcortical brain development. *NeuroImage*, *88*, 242–251. https://doi.org/10.1016/j.neuroimage.2013.09.073

Gu, Q., & Li, P. (2016). Biosynthesis of Vitamins by Probiotic Bacteria. In *Probiotics and Prebiotics in Human Nutrition and Health*. InTech. https://doi.org/10.5772/63117

Gupta, S., Allen-Vercoe, E., & Petrof, E. O. (2016). Fecal microbiota transplantation: In perspective. In *Therapeutic Advances in Gastroenterology* (Vol. 9, Issue 2, pp. 229–239). SAGE Publications Ltd. https://doi.org/10.1177/1756283X15607414

Halaweish, H. F., Boatman, S., & Staley, C. (2022). Encapsulated Fecal Microbiota Transplantation: Development, Efficacy, and Clinical Application. In *Frontiers in Cellular and Infection Microbiology* (Vol. 12). Frontiers Media S.A. https://doi.org/10.3389/fcimb.2022.826114

Hao, S., Yang, S., Zhang, N., & Cheng, H. (2023). Fecal Microbiota Transplantation Research over the Past Decade: Current Status and Trends. *Canadian Journal of Infectious Diseases and Medical Microbiology*, *2023*. https://doi.org/10.1155/2023/6981721

Heijtz, R. D., Wang, S., Anuar, F., Qian, Y., Björkholm, B., Samuelsson, A., Hibberd, M. L., Forssberg, H., & Pettersson, S. (2011). Normal gut microbiota modulates brain development and behavior. *Proceedings of the National Academy of Sciences of the United States of America*, *108*(7), 3047–3052. https://doi.org/10.1073/pnas.1010529108

Helton, S. G., & Lohoff, F. W. (2015). Serotonin pathway polymorphisms and the treatment of major depressive disorder and anxiety disorders. In *Pharmacogenomics* (Vol. 16, Issue 5, pp. 541–553). Future Medicine Ltd. https://doi.org/10.2217/pgs.15.15

Herpers, P. C. M., Neumann, J. E. C., & Staal, W. G. (2021). Treatment Refractory Internalizing Behaviour Across Disorders: An Aetiological Model for Severe Emotion Dysregulation in Adolescence. *Child Psychiatry and Human Development*, *52*(3), 515–532. https://doi.org/10.1007/s10578-020-01036-y

Hershenberg, R., Gros, D. F., & Brawman-Mintzer, O. (2014). Role of atypical antipsychotics in the treatment of generalized anxiety disorder. In *CNS Drugs* (Vol. 28, Issue 6, pp. 519–533). Springer International Publishing. https://doi.org/10.1007/s40263-014-0162-6

Hillemacher, T., Bachmann, O., Kahl, K. G., & Frieling, H. (2018). Alcohol, microbiome, and their effect on psychiatric disorders. In *Progress in Neuro-Psychopharmacology and Biological Psychiatry* (Vol. 85, pp. 105–115). Elsevier Inc. https://doi.org/10.1016/j.pnpbp.2018.04.015

Hooks, K. B., Konsman, J. P., & O'Malley, M. A. (2020). Microbiota-gut-brain research: A critical analysis. *Behavioral and Brain Sciences*, *42*. https://doi.org/10.1017/S0140525X18002133

Huang, C., Meng, D., Li, Y., Lu, S., Yang, W., Wu, B., Chen, S., Yang, Z., & Liu, H. (2023). Gut microbiota composition alteration analysis and functional categorization in children with growth hormone deficiency. *Frontiers in Pediatrics*, *11*. https://doi.org/10.3389/fped.2023.1133258

Huang, F., & Wu, X. (2021). Brain Neurotransmitter Modulation by Gut Microbiota in Anxiety and Depression. In *Frontiers in Cell and Developmental Biology* (Vol. 9). Frontiers Media S.A. https://doi.org/10.3389/fcell.2021.649103

Huang, H., Xu, H., Luo, Q., He, J., Li, M., Chen, H., Tang, W., Nie, Y., & Zhou, Y. (2019). Fecal microbiota transplantation to treat Parkinson's disease with constipation: A case report. *Medicine (United States)*, *98*(26). https://doi.org/10.1097/MD.0000000000016163

Huo, R., Zeng, B., Zeng, L., Cheng, K., Li, B., Luo, Y., Wang, H., Zhou, C., Fang, L., Li, W., Niu, R., Wei, H., & Xie, P. (2017). Microbiota modulate anxiety-like behavior and endocrine abnormalities in hypothalamic-pituitary-adrenal axis. *Frontiers in Cellular and Infection Microbiology*, *7*(NOV). https://doi.org/10.3389/fcimb.2017.00489

Inagawa, K., Hiraoka, T., Kohda, T., Yamadera, W., & Takahashi, M. (2006). Subjective effects of glycine ingestion before bedtime on sleep quality. *Sleep and Biological Rhythms*, *4*(1), 75–77. https://doi.org/10.1111/j.1479-8425.2006.00193.x

Izuno, S., Yoshihara, K., & Sudo, N. (2021). Role of gut microbiota in the pathophysiology of stress-related disorders: Evidence from neuroimaging studies. *Annals of Nutrition and Metabolism*, *77*, 4–10. https://doi.org/10.1159/000517420

Janik, R., Thomason, L. A. M., Stanisz, A. M., Forsythe, P., Bienenstock, J., & Stanisz, G. J. (2016). Magnetic resonance spectroscopy reveals oral Lactobacillus promotion of increases in brain GABA, N-acetyl aspartate and glutamate. *NeuroImage*, *125*, 988–995. https://doi.org/10.1016/j.neuroimage.2015.11.018

Jaworska, N., & MacQueen, G. (2015). Adolescence as a unique developmental period. In *Journal of Psychiatry and Neuroscience* (Vol. 40, Issue 5, pp. 291–293). Canadian Medical Association. https://doi.org/10.1503/jpn.150268

Jensen, E. A., Young, J. A., Mathes, S. C., List, E. O., Carroll, R. K., Kuhn, J., Onusko, M., Kopchick, J. J., Murphy, E. R., & Berryman, D. E. (2020). Crosstalk between the growth hormone/insulin-like growth factor-1 axis and the gut microbiome: A new frontier for microbial endocrinology. In *Growth Hormone and IGF Research* (Vols. 53–54). Churchill Livingstone. https://doi.org/10.1016/j.ghir.2020.101333

Kassam, Z., Lee, C. H., Yuan, Y., & Hunt, R. H. (2013). Fecal microbiota transplantation for clostridium difficile infection: Systematic review and meta-analysis. In *American Journal of Gastroenterology* (Vol. 108, Issue 4, pp. 500–508). https://doi.org/10.1038/ajg.2013.59

Kelly, J. R., Kennedy, P. J., Cryan, J. F., Dinan, T. G., Clarke, G., & Hyland, N. P. (2015). Breaking down the barriers: The gut microbiome, intestinal permeability and stress-related psychiatric disorders. In *Frontiers in Cellular Neuroscience* (Vol. 9, Issue OCT). Frontiers Media S.A. https://doi.org/10.3389/fncel.2015.00392

Kennedy, D. O. (2016). B vitamins and the brain: Mechanisms, dose and efficacy—A review. In *Nutrients* (Vol. 8, Issue 2). MDPI AG. https://doi.org/10.3390/nu8020068

Keshavan, M. S., Giedd, J., Lau, J. Y. F., Lewis, D. A., & Paus, T. (2014). Changes in the adolescent brain and the pathophysiology of psychotic disorders. In *The Lancet Psychiatry* (Vol. 1, Issue 7, pp. 549–558). Elsevier Ltd. https://doi.org/10.1016/S2215-0366(14)00081-9

Kiecolt-Glaser, J. K., Belury, M. A., Andridge, R., Malarkey, W. B., & Glaser, R. (2011). Omega-3 supplementation lowers inflammation and anxiety in medical students: A randomized controlled trial. *Brain, Behavior, and Immunity*, *25*(8), 1725–1734. https://doi.org/10.1016/j.bbi.2011.07.229

Knezevic, J., Starchl, C., Berisha, A. T., & Amrein, K. (2020). Thyroid-gut-axis: How does the microbiota influence thyroid function? In *Nutrients* (Vol. 12, Issue 6, pp. 1–16). MDPI AG. https://doi.org/10.3390/nu12061769

Kociszewska, D., & Vlajkovic, S. M. (2022). The Association of Inflammatory Gut Diseases with Neuroinflammatory and Auditory Disorders. In *Frontiers in Bioscience - Elite* (Vol. 14, Issue 2). Bioscience Research Institute. https://doi.org/10.31083/j.fbe1402008

Kodish, I. , R. C. & V. C. (2011). Pharmacotherapy for anxiety disorders in children and adolescents. *Dialogues Clin. Neurosci.*, *13*, 439–452.

Koh, A., De Vadder, F., Kovatcheva-Datchary, P., & Bäckhed, F. (2016). From dietary fiber to host physiology: Short-chain fatty acids as key bacterial metabolites. In *Cell* (Vol. 165, Issue 6, pp. 1332–1345). Cell Press. https://doi.org/10.1016/j.cell.2016.05.041

Konrad, K., Firk, C., & Uhlhaas, P. J. (2013). Brain development during adolescence. In *Deutsches Arzteblatt International* (Vol. 110, Issue 25, pp. 425–431). Deutscher Arzte-Verlag GmbH. https://doi.org/10.3238/arztebl.2013.0425

Kupcova, I., Danisovic, L., Grgac, I., & Harsanyi, S. (2022). Anxiety and Depression: What Do We Know of Neuropeptides? In *Behavioral Sciences* (Vol. 12, Issue 8). MDPI. https://doi.org/10.3390/bs12080262

Kwong, A. S. F., López-López, J. A., Hammerton, G., Manley, D., Timpson, N. J., Leckie, G., & Pearson, R. M. (2019). Genetic and Environmental Risk Factors Associated with Trajectories of Depression Symptoms from Adolescence to Young Adulthood. *JAMA Network Open*. https://doi.org/10.1001/jamanetworkopen.2019.6587

Lagerberg, T., Fazel, S., Sjölander, A., Hellner, C., Lichtenstein, P., & Chang, Z. (2022). Selective serotonin reuptake inhibitors and suicidal behaviour: a population-based cohort study. *Neuropsychopharmacology*, *47*(4), 817–823. https://doi.org/10.1038/s41386-021-01179-z

Lau, J. Y. F., Gregory, A. M., Goldwin, M. A., Pine, D. S., & Eley, T. C. (2007). Assessing gene-environment interactions on anxiety symptom subtypes across childhood and adolescence. *Development and Psychopathology*, *19*(4), 1129–1146. https://doi.org/10.1017/S0954579407000582

Leussis, M. P., & Andersen, S. L. (2008). Is adolescence a sensitive period for depression? Behavioral and neuroanatomical findings from a social stress model. *Synapse*, *62*(1), 22–30. https://doi.org/10.1002/syn.20462

Liu, C., Yang, S. Y., Wang, L., & Zhou, F. (2022). The gut microbiome: implications for neurogenesis and neurological diseases. In *Neural Regeneration Research* (Vol. 17, Issue 1, pp. 53–58). Wolters Kluwer Medknow Publications. https://doi.org/10.4103/1673-5374.315227

Liu, M., Nieuwdorp, M., de Vos, W. M., & Rampanelli, E. (2022). Microbial Tryptophan Metabolism Tunes Host Immunity, Metabolism, and Extraintestinal Disorders. In *Metabolites* (Vol. 12, Issue 9). MDPI. https://doi.org/10.3390/metabo12090834

Longone, P., di Michele, F., D'Agati, E., Romeo, E., Pasini, A., & Rupprecht, R. (2011). Neurosteroids as neuromodulators in the treatment of anxiety disorders. In *Frontiers in Endocrinology* (Vol. 2, Issue OCT). https://doi.org/10.3389/fendo.2011.00055

Maeng, L. Y., & Beumer, A. (2023). Never fear, the gut bacteria are here: Estrogen and gut microbiome-brain axis interactions in fear extinction. *International Journal of Psychophysiology*, *189*, 66–75. https://doi.org/10.1016/j.ijpsycho.2023.05.350

Malan-Muller, S., Valles-Colomer, M., Raes, J., Lowry, C. A., Seedat, S., & Hemmings, S. M. J. (2018a). The gut microbiome and mental health: Implications for anxiety- and trauma-related disorders. In *OMICS A Journal of Integrative Biology* (Vol. 22, Issue 2, pp. 90–107). Mary Ann Liebert Inc. https://doi.org/10.1089/omi.2017.0077

Malan-Muller, S., Valles-Colomer, M., Raes, J., Lowry, C. A., Seedat, S., & Hemmings, S. M. J. (2018b). The gut microbiome and mental health: Implications for anxiety- and trauma-related disorders. In *OMICS A Journal of Integrative Biology* (Vol. 22, Issue 2, pp. 90–107). Mary Ann Liebert Inc. https://doi.org/10.1089/omi.2017.0077

Marceau, K., Ruttle, P. L., Shirtcliff, E. A., Essex, M. J., & Susman, E. J. (2015). Developmental and contextual considerations for adrenal and gonadal hormone functioning during adolescence: Implications for adolescent mental health. *Developmental Psychobiology*, *57*(6), 742–768. https://doi.org/10.1002/dev.21214

McCormick, C. M., & Mathews, I. Z. (2007). HPA function in adolescence: Role of sex hormones in its regulation and the enduring consequences of exposure to stressors. In *Pharmacology Biochemistry and Behavior* (Vol. 86, Issue 2, pp. 220–233). https://doi.org/10.1016/j.pbb.2006.07.012

McVey Neufeld, K. A., Luczynski, P., Dinan, T. G., & Cryan, J. F. (2016). Reframing the teenage wasteland: Adolescent microbiota-gut-brain axis. In *Canadian Journal of Psychiatry* (Vol. 61, Issue 4, pp. 214–221). SAGE Publications Inc. https://doi.org/10.1177/0706743716635536

McVey Neufeld, K. A., Luczynski, P., Seira Oriach, C., Dinan, T. G., & Cryan, J. F. (2016). What's bugging your teen?—The microbiota and adolescent mental health. In *Neuroscience and Biobehavioral Reviews* (Vol. 70, pp. 300–312). Elsevier Ltd. https://doi.org/10.1016/j.neubiorev.2016.06.005

Milaneschi, Y., Hoogendijk, W., Lips, P., Heijboer, A. C., Schoevers, R., Van Hemert, A. M., Beekman, A. T. F., Smit, J. H., & Penninx, B. W. J. H. (2014). The association between low vitamin D and depressive disorders. *Molecular Psychiatry*, *19*(4), 444–451. https://doi.org/10.1038/mp.2013.36

Misiak, B., Łoniewski, I., Marlicz, W., Frydecka, D., Szulc, A., Rudzki, L., & Samochowiec, J. (2020). The HPA axis dysregulation in severe mental illness: Can we shift the blame to gut microbiota? In *Progress in Neuro-Psychopharmacology and Biological Psychiatry* (Vol. 102). Elsevier Inc. https://doi.org/10.1016/j.pnpbp.2020.109951

Murciano-brea, J., Garcia-montes, M., Geuna, S., & Herrera-rincon, C. (2021). Gut microbiota and neuroplasticity. In *Cells* (Vol. 10, Issue 8). MDPI. https://doi.org/10.3390/cells10082084

Nasir, M., Trujillo, D., Levine, J., Dwyer, J. B., Rupp, Z. W., & Bloch, M. H. (2020). Glutamate Systems in DSM-5 Anxiety Disorders: Their Role and a Review of Glutamate and GABA Psychopharmacology. In *Frontiers in Psychiatry* (Vol. 11). Frontiers Media S.A. https://doi.org/10.3389/fpsyt.2020.548505

Norton, P. J., & Barrera, T. L. (2012). Transdiagnostic versus diagnosis-specific CBT for anxiety disorders: A preliminary randomized controlled noninferiority trial. *Depression and Anxiety*, *29*(10), 874–882. https://doi.org/10.1002/da.21974

O'Hara, A. M., & Shanahan, F. (2006). The gut flora as a forgotten organ. In *EMBO Reports* (Vol. 7, Issue 7, pp. 688–693). https://doi.org/10.1038/sj.embor.7400731

Ollmann, T. M., Voss, C., Venz, J., Seidl, E., Hoyer, J., Kische, H., Pieper, L., Schiele, M. A., Domschke, K., & Beesdo-Baum, K. (2021). The interaction of 5-HTT variation, recent stress, and resilience on current anxiety levels in adolescents and young adults from the general population. *Depression and Anxiety*, *38*(3), 318–327. https://doi.org/10.1002/da.23101

Otto, M. W., Roy-Byrne, P. P., Coplan, J. D., Rothbaum, B. O., Simon, N. M., & Gorman, J. M. (n.d.). *Mark H Novel Treatment Approaches for Refractory Anxiety Disorders*.

Ozdemir, P. G., Karadag, A. S., Selvi, Y., Boysan, M., Bilgili, S. G., Aydin, A., & Onder, S. (2014). Assessment of the effects of antihistamine drugs on mood, sleep quality, sleepiness, and dream anxiety. *International Journal of Psychiatry in Clinical Practice*, *18*(3), 161–168. https://doi.org/10.3109/13651501.2014.907919

Paus, T., Keshavan, M., & Giedd, J. N. (2008). Why do many psychiatric disorders emerge during adolescence? In *Nature Reviews Neuroscience* (Vol. 9, Issue 12, pp. 947–957). https://doi.org/10.1038/nrn2513

Porcari, S., Benech, N., Valles-Colomer, M., Segata, N., Gasbarrini, A., Cammarota, G., Sokol, H., & Ianiro, G. (2023). Key determinants of success in fecal microbiota transplantation: From microbiome to clinic. In *Cell Host and Microbe* (Vol. 31, Issue 5, pp. 712–733). Cell Press. https://doi.org/10.1016/j.chom.2023.03.020

Reigstad, C. S., Salmonson, C. E., Rainey, J. F., Szurszewski, J. H., Linden, D. R., Sonnenburg, J. L., Farrugia, G., & Kashyap, P. C. (2015). Gut microbes promote colonic serotonin production through an effect of short-chain fatty acids on enterochromaffin cells. *FASEB Journal*, *29*(4), 1395–1403. https://doi.org/10.1096/fj.14-259598

Rogers, G. B., Keating, D. J., Young, R. L., Wong, M. L., Licinio, J., & Wesselingh, S. (2016). From gut dysbiosis to altered brain function and mental illness: Mechanisms and pathways. In *Molecular Psychiatry* (Vol. 21, Issue 6, pp. 738–748). Nature Publishing Group. https://doi.org/10.1038/mp.2016.50

Romeo, R. D. (2010). Adolescence: A central event in shaping stress reactivity. *Developmental Psychobiology*, *52*(3), 244–253. https://doi.org/10.1002/dev.20437

Romeo, R. D., & Romeo, R. D. (2003). Puberty: A Period of Both Organizational and Activational Effects of Steroid Hormones On Neurobehavioural Development. In *Journal of Neuroendocrinology* (Vol. 15).

Round, J. L., & Mazmanian, S. K. (2009). The gut microbiota shapes intestinal immune responses during health and disease. In *Nature Reviews Immunology* (Vol. 9, Issue 5, pp. 313–323). https://doi.org/10.1038/nri2515

Roy-Byrne, P. (2015). *Treatment-refractory anxiety; definition, risk factors, and treatment challenges*. www.dialogues-cns.org

Rudzki, L., Stone, T. W., Maes, M., Misiak, B., Samochowiec, J., & Szulc, A. (2021). Gut microbiota-derived vitamins – underrated powers of a multipotent ally in psychiatric health and disease. In *Progress in Neuro-Psychopharmacology and Biological Psychiatry* (Vol. 107). Elsevier Inc. https://doi.org/10.1016/j.pnpbp.2020.110240

Savitz, J. (2017). Role of kynurenine metabolism pathway activation in major depressive disorders. In *Current Topics in Behavioral Neurosciences* (Vol. 31, pp. 249–268). Springer Verlag. https://doi.org/10.1007/7854_2016_12

Schaeuffele, C., Schulz, A., Knaevelsrud, C., Renneberg, B., & Boettcher, J. (2021). CBT at the Crossroads: The Rise of Transdiagnostic Treatments. In *International Journal of Cognitive Therapy* (Vol. 14, Issue 1, pp. 86–113). Springer Science and Business Media Deutschland GmbH. https://doi.org/10.1007/s41811-020-00095-2

Schippa, S., & Conte, M. P. (2014). Dysbiotic events in gut microbiota: Impact on human health. In *Nutrients* (Vol. 6, Issue 12, pp. 5786–5805). MDPI AG. https://doi.org/10.3390/nu6125786

Schmidt, K., Cowen, P. J., Harmer, C. J., Tzortzis, G., Errington, S., & Burnet, P. W. J. (2015). Prebiotic intake reduces the waking cortisol response and alters emotional bias in healthy volunteers. *Psychopharmacology*, *232*(10), 1793–1801. https://doi.org/10.1007/s00213-014-3810-0

Sears, S. M. S., & Hewett, S. J. (2021). Influence of glutamate and GABA transport on brain excitatory/inhibitory balance. In *Experimental Biology and Medicine* (Vol. 246, Issue 9, pp. 1069–1083). SAGE Publications Inc. https://doi.org/10.1177/1535370221989263

Ser, H. L., Letchumanan, V., Goh, B. H., Wong, S. H., & Lee, L. H. (2021). The Use of Fecal Microbiome Transplant in Treating Human Diseases: Too Early for Poop? In *Frontiers in Microbiology* (Vol. 12). Frontiers Media S.A. https://doi.org/10.3389/fmicb.2021.519836

Settanni, C. R., Ianiro, G., Bibbò, S., Cammarota, G., & Gasbarrini, A. (2021). Gut microbiota alteration and modulation in psychiatric disorders: Current evidence on fecal microbiota transplantation. In *Progress in Neuro-Psychopharmacology and Biological Psychiatry* (Vol. 109). Elsevier Inc. https://doi.org/10.1016/j.pnpbp.2021.110258

Simkin, D. R. (2019). Microbiome and Mental Health, Specifically as It Relates to Adolescents. In *Current Psychiatry Reports* (Vol. 21, Issue 9). Current Medicine Group LLC 1. https://doi.org/10.1007/s11920-019-1075-3

Simopoulos, A. P. (2002). *The importance of the ratio of omega-6/omega-3 essential fatty acids*. www.elsevier.com/locate/biopha

Simpson, C. A., Diaz-Arteche, C., Eliby, D., Schwartz, O. S., Simmons, J. G., & Cowan, C. S. M. (2021). The gut microbiota in anxiety and depression – A systematic review. In *Clinical Psychology Review* (Vol. 83). Elsevier Inc. https://doi.org/10.1016/j.cpr.2020.101943

Sjöstedt, P., Enander, J., & Isung, J. (2021). Serotonin Reuptake Inhibitors and the Gut Microbiome: Significance of the Gut Microbiome in Relation to Mechanism of Action, Treatment Response, Side Effects, and Tachyphylaxis. *Frontiers in Psychiatry*, *12*. https://doi.org/10.3389/fpsyt.2021.682868

Soto, M., Herzog, C., Pacheco, J. A., Fujisaka, S., Bullock, K., Clish, C. B., & Kahn, C. R. (2018). Gut microbiota modulate neurobehavior through changes in brain insulin sensitivity and metabolism. *Molecular Psychiatry*, *23*(12), 2287–2301. https://doi.org/10.1038/s41380-018-0086-5

Sovijit, W. N., Sovijit, W. E., Pu, S., Usuda, K., Inoue, R., Watanabe, G., Yamaguchi, H., & Nagaoka, K. (2021). Ovarian progesterone suppresses depression and anxiety-like behaviors by increasing the Lactobacillus population of gut microbiota in ovariectomized mice. *Neuroscience Research*, *168*, 76–82. https://doi.org/10.1016/j.neures.2019.04.005

Sowell, E. R., Thompson, P. M., Tessner, K. D., & Toga, A. W. (2001). *Mapping Continued Brain Growth and Gray Matter Density Reduction in Dorsal Frontal Cortex: Inverse Relationships during Postadolescent Brain Maturation*.

Spear, L. P. (2011). Rewards, aversions and affect in adolescence: Emerging convergences across laboratory animal and human data. In *Developmental Cognitive Neuroscience* (Vol. 1, Issue 4, pp. 390–403). Elsevier Ltd. https://doi.org/10.1016/j.dcn.2011.08.001

Spear, L. P. (2013). Adolescent neurodevelopment. In *Journal of Adolescent Health* (Vol. 52, Issue 2 SUPPL.2). https://doi.org/10.1016/j.jadohealth.2012.05.006

Steenbergen, L., Sellaro, R., van Hemert, S., Bosch, J. A., & Colzato, L. S. (2015). A randomized controlled trial to test the effect of multispecies probiotics on cognitive reactivity to sad mood. *Brain, Behavior, and Immunity*, *48*, 258–264. https://doi.org/10.1016/j.bbi.2015.04.003

Stein, M. B., Schork, N. J., & Gelernter, J. (2008). Gene-by-environment (serotonin transporter and childhood maltreatment) interaction for anxiety sensitivity, an intermediate phenotype for anxiety disorders. *Neuropsychopharmacology*, *33*(2), 312–319. https://doi.org/10.1038/sj.npp.1301422

Stemmelin, J., Cohen, C., Terranova, J. P., Lopez-Grancha, M., Pichat, P., Bergis, O., Decobert, M., Santucci, V., Françon, D., Alonso, R., Stahl, S. M., Keane, P., Avenet, P., Scatton, B., Le Fur, G., & Griebel, G. (2008). Stimulation of the β3-adrenoceptor as a novel treatment strategy for anxiety and depressive disorders. *Neuropsychopharmacology*, *33*(3), 574–587. https://doi.org/10.1038/sj.npp.1301424

Sturman, D. A., & Moghaddam, B. (2011). The neurobiology of adolescence: Changes in brain architecture, functional dynamics, and behavioral tendencies. In *Neuroscience and Biobehavioral Reviews* (Vol. 35, Issue 8, pp. 1704–1712). https://doi.org/10.1016/j.neubiorev.2011.04.003

Tambaro, S., & Bortolato, M. (n.d.). *Cannabinoid-related agents in the treatment of anxiety disorders: current knowledge and future perspectives*.

Tarikere Satyanarayana, P., Suryanarayana, R., Theophilus Yesupatham, S., Reddy, S., & Reddy, N. (2023). Is Sunshine Vitamin Related to Adolescent Depression? A Cross-Sectional Study of Vitamin D Status and Depression Among Rural Adolescents. *Cureus*. https://doi.org/10.7759/cureus.34639

Taylor, A. M., & Holscher, H. D. (2020a). A review of dietary and microbial connections to depression, anxiety, and stress. In *Nutritional Neuroscience* (Vol. 23, Issue 3, pp. 237–250). Taylor and Francis Ltd. https://doi.org/10.1080/1028415X.2018.1493808

Taylor, A. M., & Holscher, H. D. (2020b). A review of dietary and microbial connections to depression, anxiety, and stress. In *Nutritional Neuroscience* (Vol. 23, Issue 3, pp. 237–250). Taylor and Francis Ltd. https://doi.org/10.1080/1028415X.2018.1493808

Unger, M. M., Spiegel, J., Dillmann, K. U., Grundmann, D., Philippeit, H., Bürmann, J., Faßbender, K., Schwiertz, A., & Schäfer, K. H. (2016). Short chain fatty acids and gut microbiota differ between patients

with Parkinson's disease and age-matched controls. *Parkinsonism and Related Disorders*, *32*, 66–72. https://doi.org/10.1016/j.parkreldis.2016.08.019

Valizadeh, M., & Valizadeh, N. (2011). Obsessive compulsive disorder as early manifestation of b12 deficiency. *Indian Journal of Psychological Medicine*, *33*(2), 203–204. https://doi.org/10.4103/0253-7176.92051

Vijay, N., & Morris, M. E. (2014). *Role of Monocarboxylate Transporters in Drug Delivery to the Brain.*

Wang, X., Yu, J., & Zhang, X. (2022). Dietary Polyphenols as Prospective Natural-Compound Depression Treatment from the Perspective of Intestinal Microbiota Regulation. In *Molecules* (Vol. 27, Issue 21). MDPI. https://doi.org/10.3390/molecules27217637

Westfall, S., Lomis, N., Kahouli, I., Dia, S. Y., Singh, S. P., & Prakash, S. (2017). Microbiome, probiotics and neurodegenerative diseases: deciphering the gut brain axis. In *Cellular and Molecular Life Sciences* (Vol. 74, Issue 20, pp. 3769–3787). Birkhauser Verlag AG. https://doi.org/10.1007/s00018-017-2550-9

Wiley, N. C., Dinan, T. G., Ross, R. P., Stanton, C., Clarke, G., & Cryan, J. F. (2017). The microbiota-gut-brain axis as a key regulator of neural function and the stress response: Implications for human and animal health. *Journal of Animal Science*, *95*(7), 3225–3246. https://doi.org/10.2527/jas2016.1256

Wolosker, H., & Balu, D. T. (2020). d-Serine as the gatekeeper of NMDA receptor activity: implications for the pharmacologic management of anxiety disorders. In *Translational Psychiatry* (Vol. 10, Issue 1). Springer Nature. https://doi.org/10.1038/s41398-020-00870-x

Yahfoufi, N., Matar, C., & Ismail, N. (2020a). Adolescence and aging: Impact of adolescence inflammatory stress and microbiota alterations on brain development, aging, and neurodegeneration. *Journals of Gerontology - Series A Biological Sciences and Medical Sciences*, *75*(7), 1251–1257. https://doi.org/10.1093/gerona/glaa006

Yahfoufi, N., Matar, C., & Ismail, N. (2020b). Adolescence and aging: Impact of adolescence inflammatory stress and microbiota alterations on brain development, aging, and neurodegeneration. *Journals of Gerontology - Series A Biological Sciences and Medical Sciences*, *75*(7), 1251–1257. https://doi.org/10.1093/gerona/glaa006

Yamamoto, E. A., & Jørgensen, T. N. (2020). Relationships Between Vitamin D, Gut Microbiome, and Systemic Autoimmunity. In *Frontiers in Immunology* (Vol. 10). Frontiers Media S.A. https://doi.org/10.3389/fimmu.2019.03141

Yarandi, S. S., Peterson, D. A., Treisman, G. J., Moran, T. H., & Pasricha, P. J. (2016a). Modulatory effects of gut microbiota on the central nervous system: How gut could play a role in neuropsychiatric health and diseases. In *Journal of Neurogastroenterology and Motility* (Vol. 22, Issue 2, pp. 201–212). Journal of Neurogastroenterology and Motility. https://doi.org/10.5056/jnm15146

Yarandi, S. S., Peterson, D. A., Treisman, G. J., Moran, T. H., & Pasricha, P. J. (2016b). Modulatory effects of gut microbiota on the central nervous system: How gut could play a role in neuropsychiatric health and diseases. In *Journal of Neurogastroenterology and Motility* (Vol. 22, Issue 2, pp. 201–212). Journal of Neurogastroenterology and Motility. https://doi.org/10.5056/jnm15146