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THE IMPACT OF GUT MICROBIOTA ON THE PATHOPHYSIOLOGY AND MANIFESTATION OF ADHD

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ABSTRACT

Attention Deficit Hyperactivity Disorder (ADHD) is currently being thoroughly investigated by the global medical community, resulting in a deeper comprehension of the disorder. The relationship between the intestine microbiome and the human body could be a noteworthy center of advanced inquire about, especially with respect to the gut-brain association. The intestine microbiome influences metabolic, immune, and neurological forms, sending signals to the brain through different immune and neurochemical pathways. Within the past, neuropsychiatric conditions were regularly credited exclusively to modifications within the brain, ignoring the affect of the resistant and metabolic frameworks. Later studies indicate that the microbiome can influence brain functioning by creating neuroactive compounds, which can in this way impact behavior and cognitive capacities. In this setting, there's an expanding interest approximately the part the intestine microbiome plays in neurodevelopmental conditions like ADHD.

Aim of the study: The purpose of this paper is to elucidate the current state of knowledge regarding the correlation between gut microbiota and Attention Deficit Hyperactivity Disorder. It examines the pathways via which bacteria may influence the functioning of the gut-brain axis and the development and severity of symptoms of the disorder. It also delineates the most recent findings concerning the potential therapeutic modulation of gut microbiota composition as a complement to conventional ADHD treatment.

Materials and methods: A review of the literature available in the PubMed and Google Scholar database was performed, using the key words: “gut microbiome”, “gut-brain axis”, “Attention Deficit Hyperactivity Disorder”, “ADHD”, “prebiotics”, “probiotics”, “synbiotics”, “short-chain fatty acids”.

KEYWORDS

Gut Microbiome, Gut-Brain Axis, Attention Deficit Hyperactivity Disorder, ADHD, Prebiotics, Probiotics, Synbiotics, Short-Chain Fatty Acids

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1. Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is the prevalent neuropsychiatric disorder among children and adolescents and often continues into adulthood. Global figures indicate that ADHD will impact 7.2% of children under the age of 18 [1]. The documented instances of this illness continue to rise annually [2]. The etiology of ADHD is complex, involving both genetic and environmental factors.

In recent years, the interplay between gut microbiota and cerebral function has been extensively researched, and vice versa [3]. This cohesive system is referred to as the gut-brain axis. The bacteria residing in our intestines are known as gut flora. The significant impact of these bacteria on nervous system functioning is primarily mediated by neuroactive metabolite production, modulation of immunological responses, and effects on neuronal development and plasticity. Consequently, research has been conducted to examine the correlation between an imbalanced gut microbiome and the symptoms and stages of neurodevelopmental diseases such as ADHD.

Recent studies show that there could be a possible association between the gut microbiota and ADHD symptoms being expressed, specifically impulsivity, inattention, and hyperactivity. The specific mechanisms of this pathway are not yet fully understood; however, preliminary evidence suggests that the gut microbiota may act as a biomarker and possible intervention target for treatments in ADHD. Altered microbiota composition shows dysbiosis with an increased irritative microbes that may impacts on intestinal permeability. This will follow fast track translocation of bacteria leading to systemic inflammation. In return then follow systemic inflammation to challenge blood-brain barrier integrity plus elevate pro-inflammatory cytokines such as IL-6 and IFN-γ. Furthermore, dysbiosis is posited to induce oxidative stress, hence impacting brain cells and neurotransmitters linked to ADHD.

This study examines the current understanding of the association between gut microbiota and ADHD, as well as potential mechanisms of interaction within the gut-brain axis. The findings of clinical research in this domain are analyzed, and prospective future directions are delineated.

2. The intestinal microbiome - what is it and how does it work?

2.1. Definition of the intestinal microbiome and the role of the microbiome in the functioning of the body

The gut microbiome is a complex ecosystem of microorganisms that inhabit the human digestive tract along with their genetic material and metabolic products [4]. The appropriate composition of the microbiota plays an important role in many physiological processes, such as digestion, vitamin synthesis, influence on the immune system and regulation of the gut-brain axis. The intestinal microbiome may be a profoundly powerful resource of the human body, which for numerous a long time was essentially connected to the well-being of the digestive system. Ultimately, it became evident that the correct composition and work of the intestine microbiome are basic for supporting physiological balance in about all systems and organs. Among other variables, the intestine microbiome impacts the functioning of the central nervous system (CNS). This happens because of the complex web of associations between the enteric nervous system (ENS) and the CNS, in which the microbiome is significant. Their collective interaction constitutes the gut-microbiome-brain axis. The sorts of microorganisms found within the intestine and the compounds they produce straightforwardly impact the signals communicated to the brain.

The gut microbiota plays an important role in the digestive process. It supports the synthesis of vitamins, mainly B and K, and some amino acids [5]. In addition, gut microbes ferment dietary fiber, producing short-chain fatty acids (SCFAs) such as butyrate, acetate, and propionate, which in turn nourish the intestinal epithelium and strengthen the intestinal barrier [6]. Moreover, intestinal microorganisms deliver chemical substances that impact endocrine and nervous system functioning. This includes neurotransmitters like gamma-aminobutyric acid (GABA) and serotonin, which impact nerve endings within the intestine and communication courses within the gut-brain axis.

2.2. Gut-brain axis: bidirectional communication

The gut-brain axis is a complex, multi-component network of connections between the central nervous system and the gastrointestinal tract. Communication within this system is bidirectional, indicating that signals from the gastrointestinal tract can influence brain function, and conversely, activities occurring in the central nervous system affect gut function [7].

The gastrointestinal system and the brain engage in bidirectional communication essential for maintaining the body's homeostasis. Signals are transmitted through the neural network (including both the central and enteric nervous systems) as well as through hormonal and immune pathways. Disruptions in this framework lead to inconsistencies in the body's response to stress, thereby facilitating the onset of illness. Intestinal microorganisms play a crucial role in maintaining that balance by establishing the intestinal barrier, a dynamic and essential protective system [8]. This barrier consists of multiple layers, including intestinal epithelial cells (such as enterocytes), endothelial cells, and elements from the lymphatic (e.g., gut-associated lymphoid tissue or GALT), circulatory, nervous, and immune systems. This structure enables the segregation of the intestinal environment from the rest of the body, allowing certain chemicals and molecules to pass while protecting against inflammatory responses and disease development.

The effective functioning of this obstruction relies on the balance of the intestinal microbiome, which can be disrupted by adverse factors such as an inadequate diet (low in fiber, high in saturated fats and simple sugars), medication use (including non-steroidal anti-inflammatory drugs and proton pump inhibitors), antibiotic treatment, chronic stress, autoimmune disorders, or gastrointestinal issues.

Dysbiosis of the microbiota results in heightened intestinal permeability, allowing antigens to infiltrate, stimulating the GALT, and provoking inflammation [9].

The interaction among the microbiota, digestive system, and nervous system is bidirectional and continuous, enabling the body to swiftly respond to varying internal and external conditions. The nervous system regulates several physiological functions in response to stress, pain, or stimuli from internal organs, employing neurotransmitters such as serotonin and dopamine. It affects cortisol secretion, fluid production in the gastrointestinal tract, and regulates peristalsis.

Inconsistencies in the microbiota or gastrointestinal tract, such as heightened intestinal permeability, irregular motility, or an atypical immune response, might stimulate the vagus nerve, which is crucial in the gut-brain axis. Modifications within the intestine are communicated to the central nervous system via neurotransmitters, neuropeptides, microbiota metabolites (such as short-chain fatty acids - SCFAs), and indicators that reflect a compromise in the integrity of the intestinal barrier, including zonulin.

3. ADHD - clinical and neurobiological characteristics

3.1 Symptoms of ADHD: hyperactivity, impulsivity, difficulty concentrating

Attention Deficit Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder characterized by heightened emotional, cognitive, and motor activity, significantly impairing a child's ability to operate well in daily life. The primary characteristics of ADHD include impulsivity, inattention, and hyperactivity, generally referred to as the triad of ADHD symptoms [10]. The escalation of these indicators is not aligned with the child's age and developmental stage, resulting in significant obstacles in social, academic, and interpersonal domains.

Carelessness frequently manifests as a diminished attention span, distractions from external factors, difficulty maintaining focus on a single task for extended periods, a tendency to misplace or forget items, and impulsive actions executed without prior contemplation or planning. Impulsivity is frequently perceived as interrupting conversations, causing unintentional damage to objects, and exhibiting a general inability to anticipate or organize acts in relation to potential outcomes. Hyperactivity manifests as considerable difficulty remaining seated or composed, persistent fidgeting or excessive movement of limbs while seated, an overwhelming compulsion to engage in conversation, and a continual necessity for physical activity.

3.2 Neurotransmitters in ADHD

In ADHD, dysfunctions in neurotransmitter activity—chemical agents facilitating signal transmission between neurons—play a crucial role. These dysfunctions largely involve dopamine and noradrenaline, with serotonin being of lower significance. Acetylcholine and glutamate play an additional role.

Dopamine is a one of the crucial neurotransmitters in the human brain and also functions as a hormone in the circulatory system. Its influence encompasses nearly every facet of our daily activities, including pleasure sensations, mood and emotional regulation, as well as abilities related to focus, organization, and learning. It compels us to seek engagement and derive meaning from our actions. The body synthesizes

dopamine via a two-phase process. Initially, it converts tyrosine (an amino acid) derived from food into DOPA, which is subsequently transformed into dopamine. This molecule affects various body functions: it regulates pain, sleep, concentration, heart rate, and movement, and plays a significant role in the brain's reward system. Research indicates that in ADHD, reduced dopaminergic activity, especially in the prefrontal cortex and striatum, leads to problems with concentration, impulsivity, and low motivation [11].

Norepinephrine is a hormone and neurotransmitter that is crucial for functioning in both the central and peripheral nervous systems. The neurons responsible for its transmission are primarily located in the brainstem and the primary region for norepinephrine production is the locus coeruleus. Norepinephrine as a hormone is secreted by the adrenal medulla (along with adrenaline) and released into the blood in stressful situations. The effect within the body is contingent upon the type and location of activated receptors, influencing heart rate, blood pressure, glucose levels, mood, concentration, sleep, and memory, among other factors. Norepinephrine is essential in the "fight or flight" response, serving as a physiological factor that enables the body to adapt to threatening situations. While its increase enhances sharpness and mobilization, excessive levels may lead to hyperactivity and anxiety. In ADHD, impaired noradrenergic transmission in the cortical-subcortical pathways (mainly in the prefrontal cortex) may manifest itself in difficulties in focusing attention and organization [11].

The most important features of dopamine and norepinephrine in the context of ADHD are comparatively summarized in Table 1.

Table 1. Comparison of the properties of dopamine and norepinephrine in the context of ADHD

Feature	**Dopamine**	**Norepinephrine**
Primary Role	Reward, motivation, pleasure, and emotional regulation	Attention, alertness, arousal, and stress response
Brain Areas Affected	Prefrontal cortex, limbic system, basal ganglia	Prefrontal cortex, locus coeruleus, brainstem
Function in ADHD	Deficiency linked to lack of motivation, impulsivity, emotional dysregulation	Deficiency linked to inattentiveness, poor focus, and low mental alertness
Clinical Signs of Deficiency	Apathy, low drive, poor emotional control, reward-seeking behavior	Distractibility, fatigue, difficulty sustaining attention
Stimulant Medication Effect	Increases dopamine availability (e.g., via blocking reuptake transporters)	Also increases norepinephrine (dual action in many stimulants)
Key Medications	Methylphenidate, amphetamine-based drugs	Same as dopamine-targeting stimulants; also atomoxetine (non-stimulant)
Receptor Types Involved	D1-D5 dopamine receptors	α1 and α2 adrenergic receptors
Side Effects When Elevated	Hyperactivity, insomnia, anxiety	Hypertension, agitation, panic symptoms
Analogy	The *"gas pedal"* — drives motivation and action	The *"steering wheel"* — directs attention and focus

Serotonin is a neurotransmitter that regulates mood, sleep, appetite, and emotions, functioning to suppress impulsivity and violence. Disruptions in the serotonin regulatory system may accompany ADHD, and the role of serotonin in ADHD is indicated by the frequent presence of mood disorders in these individuals [12].

An increasing volume of research suggests that acetylcholine and glutamate also significantly, albeit more subtly than discussed above, influence the cognitive and behavioral characteristics associated with ADHD [11]. Acetylcholine is involved in the regulation of attention, memory, learning and vigilance, while glutamate is the major excitatory neurotransmitter in the CNS, crucial for neuroplasticity, learning and memory.

The primary intervention for ADHD is non-pharmacological treatment, encompassing a multimodal strategy that addresses the psychological, behavioral, and educational or occupational requirements of the child and their family. In moderate to severe cases, pharmacotherapy is frequently administered simultaneously. Drugs used to treat ADHD directly affect neurotransmission in the brain, primarily the dopamine and norepinephrine discussed above. Methylphenidate, a stimulant, functions by obstructing the absorption of dopamine and norepinephrine, resulting in elevated concentrations of these neurotransmitters in the synapses of the prefrontal cortex and striatum [13]. It is the first-line pharmacotherapy for ADHD. The second medication commonly prescribed for ADHD is atomoxetine, a norepinephrine reuptake inhibitor [14]. It elevates norepinephrine concentrations in the prefrontal cortex, where it modulates attention and impulse control. It is not a psychostimulant.

3.3 Known risk factors and possible biological mechanisms

The primary causes of ADHD encompass genetic influences and anatomical and functional discrepancies in the brain. The disorder is affected by distinct patterns of information processing, neurometabolic anomalies, neurodevelopmental deficits, alongside the impact of both prenatal and environmental influences. It is believed that ADHD is associated with dysfunctions in multiple brain regions. Individuals with the disorder exhibit structural changes in regions such as the prefrontal cortex, striatum, basal ganglia, occipital lobe, and the cerebellum—particularly in its central region, referred to as the cerebellar vermis.

Patients with ADHD exhibit reduced brain volume, particularly in gray matter, along with a thinner cerebral cortex in the frontal, temporal, occipital, and motor regions. Additionally the caudate nuclei—elements of the basal ganglia—demonstrate reduced gray matter volume in persons with ADHD, irrespective of sex. This region, which operates in close conjunction with the prefrontal cortex, is involved in regulating behavior, learning activities, and attention.

A reduced length of the caudate nucleus is associated with hyperactivity, challenges in task organization, and diminished frustration tolerance. Impairments in reaction inhibition indicate a dysfunction of the prefrontal cortex, which regulates attention. Furthermore, diminished activity within the motor cortex contributes to the disintegration of inhibitory processes. Many symptoms characteristic of ADHD, such as impulsivity and poor behavioral regulation, align with manifestations of frontal lobe dysfunction.

4. Microbiome and Brain Function

4.1. Production of neurotransmitters and metabolites by gut bacteria

The gut–brain axis is a bidirectional communication network integrating metabolic, immunological, neurohormonal, and neuronal signals between the gastrointestinal tract and the CNS. One of the key mechanisms within this axis is the ability of the gut microbiota to produce neuroactive chemical compounds, such as neurotransmitters and metabolites, which influence brain function and behavior. In recent years, accumulating evidence has indicated that disturbances in microbiota composition may play a role in the pathophysiology of neuropsychiatric disorders, including ADHD [15].

Dopamine plays a crucial role in reward mechanisms, motivation, and executive function control. Dysregulation of dopaminergic pathways, particularly within the prefrontal cortex and basal ganglia, constitutes one of the primary pathophysiological substrates of ADHD. Gut microorganisms, including *Bacillus* and *Serratia*, are capable of synthesizing dopamine and modulating its levels via the production of enzymes involved in the metabolism of its precursors. Additionally, some bacteria influence the expression of dopaminergic receptors and the dopamine transporter within the brain.

It is estimated that approximately 90% of the body's serotonin is synthesized in the gastrointestinal tract by enterochromaffin cells under the influence of the gut microbiota [16]. Bacteria such as *Enterococcus, Streptococcus, Escherichia*, and *Candida* can directly synthesize serotonin precursors or modulate its biosynthesis by regulating the availability of tryptophan—an essential amino acid required for 5-HT production. A deficiency of serotonin within the CNS has been associated with mood disorders, aggression, and impulsivity, which frequently co-occur with ADHD.

γ-Aminobutyric acid (GABA) is the primary inhibitory neurotransmitter in the CNS, playing a fundamental role in regulating neuronal excitability, anxiety, and impulse control—functions that are impaired in ADHD. Studies have demonstrated that certain strains of gut bacteria, primarily from the *Lactobacillus* and *Bifidobacterium* genera, possess the ability to synthesize GABA via the decarboxylation of glutamic acid [17]. In animal models, administration of *Lactobacillus rhamnosus* has been shown to modulate the expression of GABA receptors in the cerebral cortex and amygdala, reducing anxiety-related and impulsive behaviors. In patients with ADHD, decreased GABA levels have been observed in the cerebrospinal fluid and prefrontal cortex, which may be indirectly associated with microbiota disturbances.

Through the fermentation of undigested carbohydrates, the gut microbiota produces SCFAs, among which acetate, propionate, and butyrate are most prominent [18]. Notably, butyrate exhibits neuroprotective, anti-inflammatory properties and modulates gene expression in the brain by affecting histone acetylation. In ADHD animal models, SCFA supplementation has been shown to improve behaviors associated with impulsivity and hyperactivity [18].

4.2. Impact of the Microbiome on Inflammation and the Blood–Brain Barrier

Disturbances in gut microbiota composition can induce chronic inflammation and increase blood–brain barrier (BBB) permeability, which is of significant importance in the pathogenesis of neuropsychiatric disorders, including ADHD [19]. Under physiological conditions, a balanced gut microbiota supports immune homeostasis by limiting the activation of pro-inflammatory pathways. Conversely, dysbiosis contributes to the development of low-grade inflammation through excessive activation of Toll-like receptors (TLRs), particularly TLR4, which recognizes lipopolysaccharides (LPS) from Gram-negative bacteria [20]. TLR4 activation results in the release of pro-inflammatory cytokines such as interleukin-6 (IL-6), interleukin-1β (IL-1β), and tumor necrosis factor-alpha (TNF-α), which can either cross into the central nervous system or trigger neuroinflammatory responses [20].

Clinical and preclinical studies have demonstrated that patients with ADHD present with elevated serum levels of inflammatory markers and an altered cytokine profile, potentially linked to microbiota dysfunction and chronic activation of the gut–brain axis [21]. Lipopolysaccharides play a crucial role as well, as increased intestinal epithelial permeability facilitates their translocation into circulation, activating the immune system and promoting chronic neuroinflammation [20]. Moreover, the function of the blood–brain barrier, whose essential role is to maintain the homeostasis of the neuronal environment by protecting the CNS from harmful substances and pathogens, is also disrupted [19]. Its integrity depends on the proper function of tight junction proteins such as claudin-5, occludin, and zonula occludens-1 (ZO-1) [19]. Animal model studies involving microbiota-depleted specimens have demonstrated reduced expression of these proteins and increased BBB permeability, which was restored upon microbiota reconstitution [19].

Bacterial metabolites, particularly SCFAs — including butyrate, acetate, and propionate — play a key role by enhancing BBB integrity through upregulating tight junction protein expression and limiting pro-inflammatory cytokine production [18]. SCFAs also modulate microglial and astrocytic activity, reducing their inflammatory activation and promoting neuroprotective phenotypes [18].

4.3. The Role of the Microbiome in Nervous System Development

The development of the CNS is a multistep process influenced by genetic, environmental, and immunological factors [22]. Increasing evidence suggests that the gut microbiota is a significant modulator of neurogenesis, synaptogenesis, and neuroplasticity, acting via the gut–brain axis [22], [23]. Intestinal dysbiosis, particularly during critical periods of neurodevelopment, may impair neurocognitive and emotional functions, contributing to neurodevelopmental disorders such as ADHD [15].

The microbiota plays its most pivotal role in the perinatal and early childhood period, when neuronal structures responsible for attention control, impulsivity, and emotional regulation — functions particularly disrupted in ADHD — are being established. Studies have shown that children born via cesarean section or fed artificial formula display a distinct microbiota composition and an increased risk of ADHD symptoms. Early-life disturbances in gut microbiota can influence the expression of genes associated with synaptogenesis and the maturation of the hypothalamic–pituitary–adrenal (HPA) axis, which is crucial for stress response regulation in individuals with ADHD [24].

Dysbiosis characterized by a reduced abundance of butyrate- and propionate-producing bacteria is associated with impaired neuroplasticity and cognitive functions in children with ADHD. These bacterial metabolites play a key role in modulating the expression of neurotrophic factors, including brain-derived neurotrophic factor (BDNF), deficiencies of which have been observed in patients with ADHD [18].

An additional important aspect is the association of intestinal dysbiosis with excessive activation of the immune system and chronic low-grade inflammation [20]. Pro-inflammatory cytokines, such as IL-6 and TNF-α, can influence the function of microglia — the brain's resident immune cells responsible for synaptic pruning and remodeling of neuronal connections during maturation [20]. The excessive microglial activation observed in ADHD studies may be partially dependent on microbiota composition and its metabolites, as confirmed by animal models of induced dysbiosis, in which ADHD-like symptoms are exacerbated [20].

5. Potential Mechanisms of Microbiome Influence on ADHD

5.1. Metabolic Disturbances and Impact on Neurotransmission

An increasing number of studies indicate that disturbances in the composition and metabolic activity of the gut microbiota may not only contribute to the development of ADHD but also modulate its clinical course, affecting the dynamics and severity of symptoms [15]. Intestinal dysbiosis influences neurobiochemical and immunological processes, which can determine the diverse presentation of ADHD symptoms and modify patient responses to pharmacotherapy and behavioral interventions [15].

Metabolic irregularities caused by dysbiosis can modulate the function of neurotransmitter systems in a manner dependent on the type and character of ADHD symptoms. For example, reduced synthesis of GABA and increased levels of glutamatergic metabolites in the brain, resulting from abnormal microbiota activity, may lead to heightened hyperactivity and impulsivity. Meanwhile, a deficiency of serotonin, associated with disrupted tryptophan metabolism by the microbiota, is linked to increased emotional lability and affective reactivity, often observed in ADHD, particularly in inattentive-type presentations.

An especially interesting mechanism involves the effects of microbial metabolites, such as SCFAs, on neuroplasticity and synaptic mechanisms of learning [18]. Animal model studies indicate that lowered SCFA levels are associated with deficits in memory and attention processes, potentially explaining the greater cognitive difficulties experienced by ADHD patients with concurrent dysbiosis [18].

Studies have also shown that children with ADHD exhibit a distinct microbiota profile compared to healthy peers — with a higher prevalence of Bacteroides species and a reduced abundance of Faecalibacterium, a genus known for its anti-inflammatory properties and role in SCFA production [15] [18]. This microbiota profile may predispose individuals to chronic low-grade inflammation, which correlates with the severity of behavioral symptoms and attention deficits [15] [21].

A newly emerging area of research involves analyzing the impact of microbiota composition on ADHD treatment outcomes [15]. There is growing evidence suggesting that disturbances in gut flora may influence the metabolism of psychostimulants, such as methylphenidate, and affect patient susceptibility to side effects, including emotional instability or sleep disorders [15]. Moreover, alterations in the microbiome may modulate the body's response to diet therapy, omega-3 fatty acid supplementation, and probiotic treatments, which are increasingly being incorporated as complementary strategies in ADHD management [15].

5.2. Inflammation and Its Impact on Cognitive Function

Data from clinical and neuroimaging studies suggest that elevated levels of pro-inflammatory cytokines in both plasma and central nervous system structures may correlate with the severity of attention deficits, working memory impairments, and executive dysfunctions in individuals with ADHD [25].

Inflammation affects the ability to maintain and selectively direct attention [20]. Studies have shown that ADHD patients with elevated inflammatory markers exhibit greater difficulty filtering out distracting stimuli and reduced capacity to sustain concentration under conditions requiring selective attention [21]. Cytokines such as IL-6 and TNF-α negatively influence the functioning of prefrontal structures, which are responsible for interference control and impulse inhibition, thereby intensifying symptoms of inattention and impulsivity [20].

Working memory, crucial for processing current information and making decisions, is also significantly impacted by chronic inflammation [25]. Research findings indicate that individuals with ADHD and higher levels of pro-inflammatory cytokines show more pronounced deficits in working memory — both in terms of information retention and processing ability [21], [25]. Reduced activity of neurotrophic factors, secondary to cytokine action, may limit the neuroplastic capacity of structures such as the hippocampus and prefrontal cortex, impairing the ability to manipulate information and plan actions [26].

Inflammation has a particularly strong effect on executive functions, such as impulse control, cognitive flexibility, task initiation, and planning [25]. Individuals with ADHD and elevated inflammatory markers more frequently exhibit difficulties in anticipating the consequences of their actions, adapting to changing conditions, and in emotional self-regulation [21], [25]. Functional neuroimaging has shown that increased cytokine concentrations correlate with reduced activity in the prefrontal cortex and anterior cingulate cortex-structures responsible for executive functions, potentially contributing to a more severe and harder-to-manage ADHD clinical course [25].

5.3. Dysbiosis and Dysregulation of the HPA Axis (Stress Response)

In recent years, an increasing number of studies have highlighted the importance of the gut microbiota in regulating the function of the HPA axis, a key component of the body's stress response system [24][26]. Dysregulation of this axis, manifested by excessive or inappropriate neuroendocrine activation, may contribute to the development and persistence of neurodevelopmental disorders, including ADHD [24].

Animal model studies have demonstrated that elimination or significant alteration of the gut microbiota leads to heightened HPA axis reactivity to stress, characterized by elevated corticosterone levels and intensified anxiety-like behaviors [24]. Similar mechanisms are proposed in humans, where disturbances in microbiome composition may promote HPA axis hyperresponsiveness and altered emotional regulation in individuals with ADHD [24][26].

Abnormal activation of the HPA axis can exacerbate cognitive and behavioral symptoms characteristic of ADHD, such as impulsivity, hyperactivity, emotional lability, and executive dysfunctions [24]. Excessive cortisol secretion disrupts dopaminergic and serotonergic neurotransmission within brain structures responsible for attention and emotion regulation [26]. Moreover, chronic hyperactivation of the HPA axis may contribute to neuroinflammation and reduce neuroplasticity, impairing the nervous system's adaptive capacity in stressful conditions [24][26].

6. The effect of probiotics and prebiotics on the severity of attention deficit hyperactivity disorder symptoms – evidence from randomised and cohort studies

A systematic review including randomised controlled, cohort, observation and before-and-after studies of probiotics and synbiotics, observed a positive effect of interventions with probiotics and synbiotics on clinical symptoms of ADHD in children and adolescents aged 5–18 years [27]. Insert (*Lactobacillus rhamnosus GG*; ATCC53103) has also been associated with better emotional, social, physical, and school functioning and overall better quality of life compared with placebo. In an 8-week randomized control trial, probiotic *(L. reuteri, L. acidophilus, L. fermentum, B. bifidum*, 8×10^9/day) treatment significantly decreased the scores on ADHD-RS, lowered serum high-sensitivity C-reactive protein (hs-CRP) and enhanced plasma total antioxidant capacity (TAC). Additionally, ingestion of *Bifidobacterium bifidum* (Bf-688) in 4- to 16-year-old children prompted significant changes of the gut microbial communities, including an increased relative abundance of *Proteobacteria* and a decreased relative proportion of *Firmicutes* and *Bacteroidota*. The changes were followed by a reduction in inattention and impulsivity symptoms. A beneficial effect was also demonstrated with administration of *Lactobacillus plantarum* PS128 (3×10^{10} CFU/day), leading to a decrease in the severity of ADHD symptoms as evaluated by SNAP-IV and CPT scales, as well as in pediatric patients with comorbid Tourette syndrome. A combined synbiotic formulation (Synbiotic 2000 Forte) with 10^{10} CFU of four lactic acid bacteria strains accompanied with prebiotic ingredients (inulin, resistant starch, pectin, and oat bran) exhibited immunomodulatory effects via attenuation of inflammatory markers, also including markers of inflammatory reactions in the intestine and vascular walls. This was suggested to be mediated through an increase in SCFA levels, in particular butyrate, which are known to function as central signalling molecules of the brain-gut axis [27].

Data on microbiota interventions in adults with ADHD is scarce, but a nine-week trial of Synbiotic 2000, which combines probiotics and prebiotics, telicited improvements in emotional regulation as well as reductions in CRP and TNF-α [27]. This might be a result of gut-brain axis interaction through serotonergic system, gut barrier function, and SCFA metabolism [27]. Cognitive symptoms were unaffected, but improvements were seen with emotional and stress symptoms, indicative of effects on comorbid anxiety and affective dysregulation [27], [28]. Diet and ADHD, at least, among the areas of potential etiopathic factors that have been raised concerns an improved, probably worth recommending, dietary perspective.

7. Dietary and exclusion treatments in ADHD – the relation of dietary based neurobehavioural functioning

In the treatment, the future of elimination diets in ADHD receiving more and more attention. These measures temporarily or permanently remove certain dietary elements that are recognized to evoke neuroinflammatory, metabolic, or behavioral correlates.

One of the most well known diets in this category is the Feingold Diet, which restricts artificial food dyes, chemical preservatives, and also natural salicylates. Additives including tartrazine (E102), allura red (E129), quinoline yellow (E104) and sodium benzoate (E211) are eliminated as these are known to affect central nervous system function particularly dopaminergic and noradrenergic neurotransmission. These chemicals can also activate

mast cells and the immune system through non-IgE pathway that not only stimulate histamine (and proinflammatory cytokines, such as, TNF-α, IL-6) release, but also microglia activation. This neuroinflammatory reaction is accepted as one of the core mechanisms in the pathophysiology of ADHD.

Data from experimental studies suggest that tartrazine and sodium benzoate may increase dopamine release in the prefrontal cortex and basal ganglia; this can lead to hyperstimulation of dopaminergic pathways, alteration of the cortico-striato-thalamo-cortical loop, and potentiation of hyperactivity and impulsivity [28]. Furthermore, such exposure has been reported to suppress serotonergic transporter (SERT) activity leading to an elevated synaptic 5-hydroxytryptamine levels upsetting the serotonergic/dopaminergic systems balance in terminal areas of brain regions such as the amygdala and hippocampus. This may possibly lead to mood instability and heightened impulsivity in patients with ADHD [29]. It is consider that also sodium benzoate might be responsible for inhibition of norepinephrine reuptake through norepinephrine transporter (NET) and consequent excessive adrenergic stimulation within prefrontal cortex and executive dysfunctions [30].

Clinical trials indicate that in children with ADHD, diets with restricted elimination have the potential to reduce the symptoms both of impulsivity and inattention, as evidenced by the response rate to such interventions compared to those on tools like SNAP4IV and ADHD-RS [27]. Intervention studies also demonstrate better neuropsychological performance and decreased inflammation, adding evidence to a possible relation between certain food additives and aggravation of ADHD symptoms, especially among children with food hypersensitivity and gastrointestinal symptoms.

8. Research Challenges and Future Directions

Interest in the gut–brain axis in ADHD is increasing, though existent literature is limited by methodological shortcomings, such as small sample size, short study duration, and inconsistency in probiotic type and symptom measurement, particularly in pediatric studies [27],[31]. Children and adults do not only have distinct microbial profiles but also react differently to microbiota-targeted interventions, possibly reflecting age-specific effects of gut stability, immune responses, and neurodevelopment. Pediatric studies performing trials with *Lactobacillus rhamnosus GG* (10^{10} CFU for 3 months) show increases in emotional, physical, and school-related quality of life [27], and adult studies using synbiotics such as Synbiotic 2000 indicate improved emotional control and decreased inflammation (CRP, TNF-α) [32]. These distinctions could be explained by increased neuroplasticity and HPA axis responsiveness in children. Microbiome profiles also appear to vary with age: ADHD children are often characterized by heightened *Sutterella, Desulfovibrio* and *Alistipes*, and reduced *Bacteroides* [31], while adults have lower levels of SCFA and diminished production of tryptophan and GABA [31], [32]. These findings further justified the potential of fecal or plasma metabolite profiling (e.g., SCFAs, indole metabolites, GABA) as non-invasive biomarkers for ADHD. Due to the higher microbiome plasticity in children, they may have a greater gain from probiotic interventions [27]. However, there is urgent need for such bigger trials of proper design across age groups and which include long-term followup and integrated clinical, microbiological and metabolomic assesements to confirm the utility of gut microbiota based diagnostic or therapeutic tool for ADHD.

9. Summary

Prior research suggests a substantial role of gut microbiota in the pathophysiology of ADHD, although the mechanisms underlying this influence are not fully elucidated. Distinct alterations in microbiome composition have been seen in patients with ADHD, including diminished microbiota diversity, decreased prevalence of short-chain fatty acid (SCFA)-producing bacteria, along with modifications in dopamine metabolism and neuroinflammation. Certain bacteria, including Bifidobacterium, Odoribacter, and Bacteroides, have demonstrated potential correlations with ADHD symptoms in research including both children and adults.

Despite promising results, there is a need for further studies with larger samples, taking into account age and genetic diversity, and using uniform methods of analysis. Additionally, functional studies are necessary to better understand the mechanisms of microbiota action in ADHD. In summary, the gut microbiota is a promising area of research in the context of ADHD. Understanding its role may open new diagnostic and therapeutic possibilities, including microbiome interventions that may complement traditional treatments for this disorder.

Disclosure

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