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REVIEW

Gut microbiota and attention deficit hyperactivity disorder: new perspectives for a challenging condition

María Carmen Cenit[1,2] · Isabel Campillo Nuevo[1] · Pilar Codoñer-Franch[2,3] · Timothy G. Dinan[4,5] · Yolanda Sanz[1]

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Abstract A bidirectional communication between the gut and the brain (gut–brain axis) is well recognized with the gut microbiota viewed as a key regulator of this cross-talk. Currently, a body of preclinical and to a lesser extent epidemiological evidence supports the notion that host–microbe interactions play a key role in brain development and function and in the etiology of neurodevelopmental disorders. Early life events and shifts away from traditional lifestyles are known to impact gut microbiota composition and function and, thereby, may increase the risk of developing neurodevelopmental disorders. Attention deficit hyperactivity disorder (ADHD) is nowadays the most prevalent neurodevelopmental disorder. Despite many years of research its etiology is unclear and its diagnosis and treatment are still challenging. Different factors reported to be associated with the risk of developing ADHD and/or linked to different ADHD manifestations have also been linked to shifts in gut microbiota composition, suggesting a link between the microbiota and the disorder. Evidence from preliminary human studies also suggests that dietary components that modulate gut microbiota may also influence ADHD development or symptoms, although further studies are warranted to confirm this hypothesis. Here, we firstly review the potential mechanisms by which the gut microbiota may regulate the brain–gut axis and influence behavior and neurodevelopmental disorders. Secondly, we discuss the current knowledge about the different factors and dietary components reported to be associated with the risk of developing ADHD or its manifestations and with shifts in gut microbiota composition. Finally, we briefly highlight the need to progress our understanding regarding the role of the gut microbiota in ADHD, since this could open new avenues for early intervention and improved management of the disease.

Keywords Microbiota · ADHD · Microbiota · Gut–brain axis · Dysbiosis

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✉ María Carmen Cenit
mccenit81@gmail.com

✉ Yolanda Sanz
yolsanz@iata.csic.es

[1] Microbial Ecology, Nutrition and Health Research Group, Institute of Agrochemistry and Food Technology, National Research Council (IATA-CSIC), Avd. Agustín Escardino, 7, 46980 Paterna, Valencia, Spain

[2] Department of Pediatrics, Dr. Peset University Hospital, Avd. De Gaspar Aguilar, 80, 46017 Valencia, Spain

[3] Department of Pediatrics, Obstetrics and Gynecology, University of Valencia, Av Blasco Ibáñez, 13, 46010 Valencia, Spain

[4] APC Microbiome Institute, University College Cork, Cork, Ireland

[5] Department of Psychiatry and Neurobehavioural Science, University College Cork, Cork, Ireland

Introduction

Neurodevelopmental disorders constitute a heterogeneous group of conditions characterized by developmental deficits of the central nervous system that typically have an early onset. The cluster of neurodevelopmental conditions includes highly prevalent disorders such as autism, autism spectrum disorders, attention deficit hyperactivity disorder (ADHD) and schizophrenia among others.

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These disorders, varying from mild to severe phenotypes, lead to impairments in personal, social, academic and/or occupational functioning. The specific underlying mechanisms that bring about the development of the majority of neurodevelopmental disorders have not been fully elucidated. Although genetics has been described to play the most important role in the etiology of most of the neurodevelopmental conditions, environmental factors are also strongly believed to contribute to their development and/or manifestation [1]. ADHD is currently the most frequent neurodevelopmental and neurobehavioral disorder in childhood affecting roughly 5% of children worldwide. ADHD is characterized by developmentally inappropriate levels of hyperactivity, impulsivity and/or attention problems. The current global burden of ADHD in the society is highly significant and its prevalence is alarmingly rising over time [2]. Furthermore, ADHD is persisting in many cases into adolescence and adulthood being thus considered a life-long issue for many patients [3]. According to the fifth edition of the Diagnostic and Statistical Manual (DSM-V) based on the types of symptoms, mainly three types of ADHD presentations can occur; a hyperactive and/or impulsive subtype predominant in males, a inattentive subtype predominant in females and a combined subtype [4]. In addition, ADHD is often associated with other psychiatric comorbidities, being therefore considered as a very heterogeneous disorder [5]. It could be suggested that the effect of different combinations of genetic, environmental factors and complex gene–environment interactions may lead to divergent neurobiological alterations and in turn to different neuropsychological impairments and symptom profiles in ADHD. Thus, it has been proposed that the prominent clinical heterogeneity observed between the different subgroups of ADHD patients might be partially due to differences in the disease etiology [6].

Currently, ADHD diagnosis is based on clinical symptoms, an approach widely criticized on the grounds of reliability. In addition, ADHD treatment is currently based on a multimodal approach with the combination of psychotherapy and pharmacotherapy, but no reliable markers of treatment response have been identified yet and 20–35% of subjects in clinical trials may have an inadequate response to the treatment [7]. Furthermore, pharmacotherapy is often associated with adverse side effects [8, 9] and has shown short-term effectiveness on ADHD treatment although its long-term efficacy is still questionable. Due to these concerns, many families choose not to use pharmacotherapies to treat ADHD, and even when pharmacotherapy is used, drug holidays are recommended. Therefore, future studies would be required to identify risk factors involved in ADHD which could offer new opportunities to improve ADHD diagnosis and management.

So far, family studies, including adoption studies, have suggested a high genetic component for ADHD, showing levels of heritability comparable to other neurodevelopmental and psychiatric disorders such as schizophrenia or bipolar disorder (2- to 8-fold increased risk of ADHD in parents and siblings of children with the disease and rates of ADHD significantly higher between biological relatives compared with adoptive relatives) [10]. Twins studies have confirmed the high level of ADHD heritability ($h^2 = 0.77–0.82$), but they have also shown a 20% of discordance between monozygotic twins which indicates that environmental factors are also involved in disease development. Indeed, the contribution of environmental factors to ADHD has been estimated to be 20–30% although the exact etiological factors involved remain unknown [11]. Neurotransmission system dysfunctions (dopamine, noradrenaline and/or serotonin deficits) play an important role in the ADHD pathophysiology and its manifestations and currently the most widely used treatments for ADHD are based on targeting monoaminergic systems [12]. However, the precise underlying mechanisms that lead to these neurobiological alterations still remain unidentified. Intensive investigations by different genetic approaches carried out in recent years have had limited success in identifying associations at the critical significance level, very likely due to the high heterogeneity; a large part of ADHD heritability has yet to be defined [13]. Remarkably, most of the studies performed until now in order to decipher the etiology of ADHD have focused on the study of the influence of the human genome in the risk of developing ADHD and/or their phenotypes, overlooking the fact that our second genome, the genome of our microbiota, is also involved in brain development and function and may play a crucial role in neurotransmission and neuronal plasticity at least according to experimental evidence from animal models [14].

It is well established that the gut microbiome, the entire genome of the gut microbiota, influences host development and physiology, playing a key role in the balance between health and disease. In recent years, emerging evidence has suggested a role of the gut microbiota in brain function and behavior and, in turn, intestinal dysbiosis has been linked to different behavioral features [14]. Gut microbiota undergoes a dynamic nonrandom process of maturation until the age of 2–3 years when an adult-like microbiota structure is established. Although later in life the microbiota may still experience changes, the symbiotic link between the host and the microbiota is thought to be mainly established early in life and occurs in parallel with neurodevelopment. In fact, different evidences have demonstrated that early life perturbations of the developing gut microbiota, very vulnerable because of its high instability and immaturity, can impact neurodevelopment and potentially lead to adverse

mental health outcomes later in life [15]. Understanding the early interaction between the intestinal microbiota, the environment and the host would open new avenues for nutritional/therapeutic interventions in at-risk populations for neurodevelopmental disorders. Several preclinical studies and a few human studies have investigated the role of different probiotics in behaviors associated with psychiatric disorders with promising results. Such bacteria are termed psychobiotics (probiotics with a mental health benefit). The potential regulation of the brain–gut axis via intervention in the gut ecosystem [16] has been neglected for many years in neuropsychiatric research, but now it is being intensively explored. Nevertheless, most of the current evidence comes from animal studies and more human studies are urgently needed to move forward in this field. In particular, genomic studies in ADHD including analysis of the gut microbiome are needed, especially at early stages in life and during further neurodevelopmental periods (childhood and adolescence), where many psychiatric disorders first become evident and when the role of the microbiota and its functions could be amenable [17].

In this review, we discuss the potential mechanisms by which the gut microbiota may influence the brain–gut axis and consequently behavior and neurodevelopmental disorders such as ADHD. We also highlight the current knowledge about the different environmental factors reported to be associated with both the risk of developing ADHD or its manifestations and shifts in gut microbiota composition. The ultimate aim of the review is to identify gaps of knowledge that will be necessary to investigate for getting a better understanding of the potential role played by the gut microbiota in ADHD, since this could open new possibilities for early intervention and improved management of the disorder.

Gut microbiota mechanisms regulating gut–brain axis and behavior

Studies in animal models, where the intestinal microbiota can be easily manipulated, have provided multiple insights into how the microbiota may be involved in the development of brain-related disorders [18, 19]. It has also been established that behavioral traits can be transferred by fecal microbiota transplantation, suggesting that microbiota chances could be rather a cause than a consequence of behavioral alterations [20, 21]. Particularly, in the context of mental health, the proposed mechanisms by which the gut microbiota may modulate brain development, function and behavior include immune (cytokines), metabolic (short-chain fatty acids) endocrine (cortisol) and neural (vagus and enteric nervous system) pathways [22]. Microbiota has a substantial impact on the host metabolome and a large array of essential molecules with neuroactive functions is known to be produced by gut microbes [23]. Different bacterial strains have been shown to mediate behavioral effects via the vagus nerve as demonstrated by vagotomy in a number of preclinical studies, although not all effects depend on the vagus nerve [24]. Likewise, different mechanisms by which the brain influences gut microbiota composition have been identified [16]. Indeed, host stress hormones such as noradrenaline might influence bacterial gene expression or signaling between bacteria, and this might change the microbial composition and activity [25]. Certain bacteria including inhabitants of the intestinal tract are capable of producing different neuroactive compounds such as neurotransmitters. It has been determined that *Lactobacillus* spp. and *Bifidobacterium* spp. can produce GABA [26]; *Escherichia s*pp., *Bacillus* spp. and *Saccharomyces* spp. can produce noradrenalin; *Candida* spp., *Streptococcus* spp., *Escherichia s*pp. and *Enterococcus* spp. produce serotonin; *Bacillus* spp. produce dopamine; and *Lactobacillus s*pp. produce acetylcholine [27]. In addition, plasma serotonin levels of conventional mice have been found to be significantly higher than those in germ-free (GF) mice, which have no intestinal microbiota, demonstrating the capacity of the microbiota to influence this neurotransmitter. It has been suggested that secreted neurotransmitters from bacteria in the intestinal lumen may induce epithelial cells to release molecules such as hormones and cytokines that, in turn, have the ability to modulate neural signaling within the enteric nervous system and subsequently control brain function and behavior (18). This evidence suggests that the gut microbiota might be a therapeutic target for brain disorders mediated by deregulation in neurotransmitters such as ADHD. The dopamine and norepinephrine pathways, which project to the prefrontal cortex and striatum, are responsible for modulating cognitive control of behavior, motivation and reward perception and these pathways are known to play a central role in the pathophysiology of ADHD. However, no studies have been conducted so far to explore how these pathways may be modulated by the gut microbiota in the context of ADHD and further investigations are needed to develop and validate evidence-base therapeutic strategies targeting the microbiota for ADHD.

Tryptophan is an essential amino acid precursor to many biologically active molecules, including the neurotransmitter serotonin and metabolites of the kynurenine pathway. Only around 5% of systemic tryptophan is metabolized into serotonin and the rest is metabolized along the kynurenine pathway. This depends on the expression of two enzymes, indoleamine-2,3dioxygenase (IDO), which is found in all tissues in mammalians and in yeast, and tryptophan-2,3-dioxygenase (TDO), which is localized within the liver in mammalians and is also produced by eukaryote and

prokaryote organisms [28]. The activity of both enzymes is strongly controlled by inflammatory mediators such as cytokines and corticosteroids [29]. The kynurenine pathway is stimulated both in the periphery and in the brain under inflammatory conditions. The increased activation of these two enzymes could induce serotonin depletion and depressive mood. On the other hand, the downstream metabolites of the kynurenine pathway are neuroactive metabolites which can also modulate neurotransmission and immunity [30]. Kynurenine, kynurenic acid, xanthurenic acid, and quinolinic acid are the major downstream breakdown products of tryptophan metabolism which increase after immune stimulation. Those different metabolites have shown to play multiple and diverse effects. In this context, few years ago a study specifically showed that kynurenine, kynurenic acid, and xanthurenic acid have anti-inflammatory effects trough a reduction of IFNgamma, whereas quinolinic acid, produced mainly by activated microglia and macrophages, exerts pro-inflammatory effects further aggravating the initial inflammation (21). It is important to highlight that quinolinic acid also acts as an important neurotoxin, gliotoxin and pro-oxidant molecule [31]. Gut microbial colonization and development of the gut microbiome occur in parallel with cognitive development and overlap with the ontogeny of the serotonergic system [32]. It has been recently reported that the gut microbiota regulates the host immune system and modulates HPA axis and, therefore, glucocorticoids production, with a subsequent impact on tryptophan metabolism leading to changes in the serotonergic neurotransmission with neuropsychiatric consequences [33]. Of note, all bifidobacteria have the machinery to produce tryptophan and particularly oral ingestion of a strain of *Bifidobacterium infantis* showed to increase, as expected, the levels of the serotonin precursor, tryptophan, in the plasma of rats and potential antidepressant properties measured by the forced swim test [34]. Although a relationship between serotonin depletion and tryptophan availability has not been found in ADHD yet, further studies are awaited to explore the role of the microbiota in the balance between these neural mediators.

In addition, short-chain fatty acids (SCFAs) such as butyrate, acetate and propionate that are produced by microbial fermentation mainly from dietary fiber in the gut are known to have neuroactive properties. For instance, the administration of a high dose of propionate in rats induced a neuroinflammatory process and behavioral alterations related with neurodevelopmental disorders [35]. Propionate is also a common preservative in food products that has been demonstrated to exacerbate autism spectrum disorder symptomatology [36]. On the other hand, butyrate, via an epigenetic mechanism related to its capacity to inhibit histone deacetylase, exerts beneficial behavioral effects [37]. SCFAs also regulate immunity and this may have consequences on the central nervous system. In fact, it has been recently demonstrated that the treatment with a mix of SCFAs could rescue microglial function previously impaired in GF animals [38].

The microbiota has also been shown to modulate a range of neurotrophins and proteins involved in brain development and plasticity. Particularly, brain-derived neurotrophic factor (BDNF) is a neurotrophin known for its important effects on promoting neurogenesis and neuronal survival. Some findings clearly indicate that the gut microbiota can influence BDNF levels mainly through the effect of SCFAs and this links the microbiota to neuroplasticity-related CNS systems [24]. A reduction in the level of BDNF expression in the hippocampus of germ-free mice, as well as in mice after the administration of oral antimicrobials [24], has been shown to contribute to working-memory impairment. It has also been demonstrated that the intervention with a strain of *Bifidobacterium longum* normalizes the changes in behavior and BDNF mRNA induced by an intestinal parasite. Recent studies have shown that plasma BDNF levels in ADHD patients differ from normal controls suggesting that BDNF may play a role in its pathogenesis [39]. Although it is still not clear the extent to which the human genome and microbiome contribute to BDNF expression, there are indications that both could influence its variation. Therefore, further studies would be desired to explore whether gut microbiota could be manipulated to favorably modulate BDNF levels in the context of ADHD.

Environmental factors influencing gut microbiome composition and risk of developing ADHD

The etiology and reasons for the increasing ADHD prevalence are not fully understood, although recent evidence suggests that environmental factors might be playing a key role [11]. Recently, the risk of developing ADHD has been suggested to be associated with many perinatal risk factors, including delivery mode (vaginal delivery or cesarean section delivery), gestational age, type of feeding (breastfeeding and formula), maternal health and early life stressors among others, supporting the idea that ADHD is a multifactorial disorder triggered by certain environmental factors such as gut microbiota among others in genetically susceptible individuals [40, 41]. Of note, many of those environmental factors associated with the risk of developing ADHD are also known to influence the early gut microbiota composition (Fig.1) [42, 43]. The perinatal period is a key period in the establishment of the initial microbiota of the infant and it has been considered as a window of opportunity for influencing brain development via gut microbiota modulation [15].

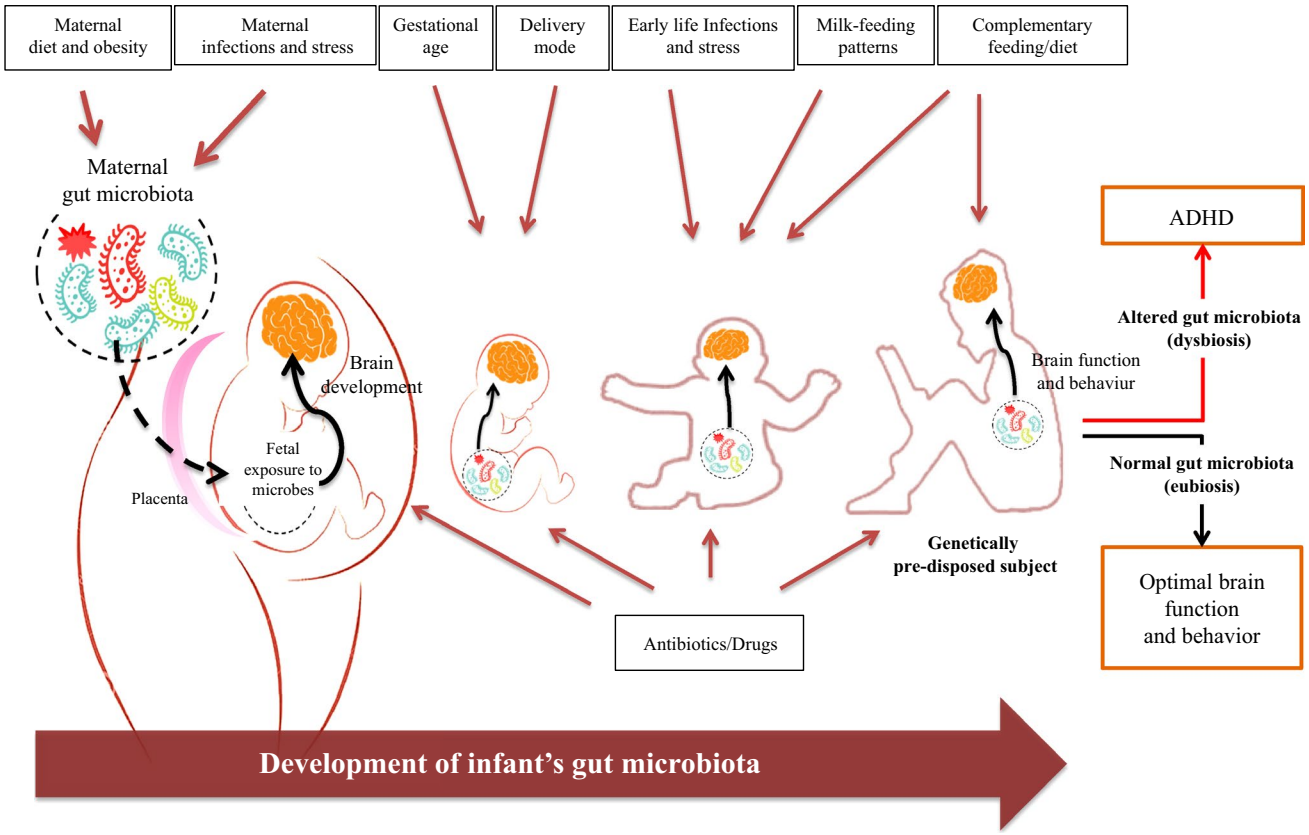

Fig. 1 Schematic representation of environmental factors that influence the development of gut microbiota in childhood. Many of these factors have also been associated with the risk of developing ADHD, suggesting a link between the microbiota and this disorder. Therefore, it is hypothesized that microbiota configuration during infancy and childhood, under the influence of different environmental factors, may have long-term consequences, protecting against or contributing to ADHD development or its manifestation

Delivery mode and gestational age

The mode of delivery (vaginal delivery or delivery by cesarean section) has a strong influence on shaping the initial gut microbiota composition. Cesarean section (C-section) correlates with decreased gut microbiota diversity and delays in colonization of *Bacteroidetes, Bifidobacterium* and *Lactobacillus* [44, 45]. In fact, the analysis of the meconium of newborn infants revealed a strong correlation between the first infant gut microbial communities and those found in either the mother's vagina in the case of vaginal delivery or the mother's skin in the case of delivery by CS [46].

Interestingly, using animal models delivery by CS has been shown to be associated with changes in dopamine response [47]. Furthermore, CS delivery compared to vaginal delivery has been linked to the risk of developing many diseases, including neurodevelopmental disorders such as autism, although confounding factors may play a role driven this association [48]. In addition, although a recent meta-analysis have not confirmed the significant effect of CS on the risk of developing ADHD [49], some individual studies have reported a link between developing the disorder and this type of delivery mode [50, 51]. Therefore, there is still a need for further studies considering confounding factors to draw more definitive conclusions about the relationship between risk of ADHD and delivery mode. In addition, significant divergences in gut microbial composition of the neonate have been found depending on the duration of pregnancy, being gestational age at birth a major driver of gut microbiota assembly in preterm neonates. Preterm neonates, who have been described to have a higher risk of developing ADHD and to have significantly more severe ADHD symptoms [52, 53], seem to lack two of the main bacterial genera present in healthy term infants, *Bifidobacterium* and *Lactobacillus* [43]. Preterm birth increases also the risk of infection which in turn is associated with the increased risk of neurodevelopmental impairment. In addition, it is well established that antibiotics use, which is related to infection, promotes a less diverse microbiota [54] and antibiotic intake and altered brain function are also associated [55].

Maternal health and early life stressors

Maternal stress during pregnancy has also been demonstrated to have profound effects on offspring, being associated with an increased incidence of neurodevelopmental disorders including ADHD [56–58]. Furthermore, children with ADHD whose mothers were exposed to moderate and severe stress during pregnancy were reported to develop more severe symptoms than children with ADHD whose mothers were not exposed to prenatal stress [58]. The exact mechanisms by which maternal stress causes developmental problems in offspring are still unclear although it is well known that chronic stress during pregnancy alters vaginal host immunity and resident microbiota composition [59] and this, in turn, could impact the microbial assembly of the neonatal gut having significant consequences for offspring development and disease risk. Maternal separation, an early life stressor that results in long-term hypothalamic–pituitary–adrenal (HPA) alterations, has been shown to have long-term effects on the microbiome composition and behavior in animal models (45). It has been hypothesized that non-genetic factors, such as early life experiences, may interact with genetic predisposition, leading to ADHD development. The development of the HPA stress axis overlaps with the early postnatal microbial colonization of the neonatal gut and the establishment of the microbiota and has been demonstrated to be sensitive to gut microbial disruption in animal models. In particular, Sudo and colleagues published that gut microbes were able to affect the postnatal development of the HPA stress response in mice, being the gut commensal microbiota required at a specific developmental stage for the HPA system to become completely susceptible to inhibitory neural regulation [60]. Glucocorticoids, the end product of HPA axis activation, are required for normal brain development. The appropriate development of the HPA axis is essential for the balanced functioning of the gut–brain axis. HPA dysregulation has been recognized as a hallmark of inflammatory and psychiatric disorders. A meta-analysis of case–control studies found significantly lower cortisol levels in children suffering from ADHD indicating a dysregulation of the HPA axis in the disorder (46). Contradictory findings have also been published. In the spontaneously hypertensive rat, an animal model of ADHD, maternal separation induced excessive activation of the HPA-mediated stress response and also affects dopamine transporter function and norepinephrine release in the hippocampus [61, 62]. It has been reported that the administration of specific strains of *Lactobacillus* and *Bifidobacterium* species seems to be able to normalize corticosterone release as well as to ameliorate colonic dysfunction and behavioural alterations induced by maternal separation, supporting the beneficial role of interventions in the gut ecosystem in restoring HPA-axis balance, at least in this model of chronic stress [60, 63].

Maternal infection, strongly linked to microbiota changes and immune activation, has also been suggested to be associated with ADHD onset in offspring [64, 65]. A preclinical study assessing the effect of maternal infection on mental health in the offspring determined that maternal immune activation could lead to a disrupted gut microbiota as well as to gut barrier dysfunction and behavioral alterations in the offspring [66]. The integrity of the adaptive immune system, and in particular T lymphocyte responses, has been shown to be crucial for normal learning and memory in mice [67]. Ceylan and co-workers found significantly higher levels of neopterin, a good indicator of cellular immunity, in ADHD compared with controls, suggesting that changes in cellular immunity may be involved in ADHD brain dysfunction [68]. Remarkably, the significant impact of the prenatal immune activation on the gut–brain axis has been shown to be reversible by the administration of *Bacteroides fragilis*, a common inhabitant of gut microbiota, to the offspring [66].

It has been demonstrated that maternal obesity and metabolic disease, including diabetes and hypertension, and unhealthy maternal diets have a long-term impact on offspring behavior and physiology [69], which may also be related to changes in gut microbiota composition induced by these conditions and the diet reported elsewhere. Different studies have suggested that maternal body mass index (BMI) and obesity prior and during pregnancy are linked to the risk of developing ADHD [70]. Rodriguez and colleagues analyzed data from three separate cohorts which examined whether pregnancy weight (BMI and/or weight gain) shows a relationship to symptoms of ADHD in offspring [71]. They found a significant association between pre-pregnancy overweight or obesity and a high ADHD symptom score in offspring while gestational weight gain was unrelated to ADHD. Evidence from animal models supports human epidemiological studies and demonstrates that maternal high-fat-diet (HFD)-induced obesity impacts behavioral programming of offspring resulting in impairments in social behavior and hyperactivity, increased anxiety and depressive behaviors and reduced cognitive development [72]. Remarkably, a recent study in mice has shown that dietary intervention can rescue maternal obesity induced behavioral deficits and neuroinflammation in offspring [72]. However, further studies in humans should be conducted to investigate the role of dietary intervention in rescuing behavioral alterations and understand whether gut microbiota modulation mediates the effects. Breast milk microbiota composition has been demonstrated to be

influenced by several factors including maternal weight [73]. Thus, the effect of maternal weight on milk microbiota, which in turn influences the offspring microbiota, could also be an additional mechanism by which the offspring behavior is modulated.

Although detailed analysis of the microbiota in patients with ADHD is lacking, there is evidence about the link between obesity and ADHD [74], and between obesity and alteration of the gut microbiota [75]. Obesity induces a low-grade inflammatory state which has been associated with behavioral and cognitive alterations, being gut microbiota most likely an important mediator between inflammation and altered behaviors [76]. Overall, data from GF mice studies, antibiotic treatment studies, and probiotic interventions suggest that alterations in gut microbiota that reduce the inflammatory state also reduce stress-related behaviors, supporting the role of the gut microbiota as a mediator between inflammation and behavioral alterations. This evidence points for a potential role of intervention in the gut ecosystem in obese mothers, mothers who experience stress during pregnancy and/or are at risk of delivering prematurely to reduce the risk of induced behavioral alterations in offspring in the future.

Infant nutrition and childhood diet

Infant nutrition in early life (mainly type of feeding, the time of the introduction of solid food and the pattern of complementary food introduced) is a key element that shapes gut microbiota composition and, remarkably, a protective role of breastfeeding in ADHD development has been suggested [77, 78]. Furthermore, diet is considered one of the most crucial factors impacting human gut microbiota composition and functionality [79] and has emerged as one of the modifiable factors that can help protect against mental health disorders. To date, many studies have reported associations between diet and the risk of developing psychiatric disorders with gut microbiota dysbiosis considered one of the important players mediating this association. Unhealthy diet is a risk factor for depression and recent evidence suggests that dietary manipulation of the gut microbiota may have significant value in preventing and treating emotional conditions [80]. In this context, a metanalysis including 22 studies investigating the protective effects of the Mediterranean-style diet on brain diseases demonstrated that higher adherence to this specific diet was associated with a reduced risk for depression and cognitive decline [81]. A recent prospective study in a large cohort showed that unhealthy maternal and early postnatal dietary patterns, independently of other potential confounding factors, elevate the risk of behavioral and emotional problems in the offspring [82]. In addition, an overall shift away from traditional lifestyles has been linked to changes in the microbiota composition as well as to the increased rates of depression and other mental health disorders including ADHD in independent studies. Diet has been proposed as one of the most important environmental factors that seem to influence the risk of developing ADHD in children and its prognosis or manifestations [83]. Specific diets have been suggested to reduce ADHD symptoms including sugar-restricted, additive/preservative-free, oligoantigenic elimination diet, and fatty acid supplements. In addition, it has been proposed that chronic deficiencies of certain minerals such as zinc, iron, magnesium and iodine and insufficient dietary intake of long-chain polyunsaturated fatty acids (PUFAs) may have a significant impact on the development and symptoms of ADHD in children [83].

Few years ago a study showed considerable improvement effects of a restricted elimination diet in a group of children with ADHD [84]. In addition, a recent systematic review and meta-analysis indicated that artificial food color exclusion, and to a lesser extent free fatty acid supplementation, significantly reduce symptom severity in ADHD [85]. Nowadays, it is still unclear how both artificial food coloring and free fatty acids could impact ADHD outcomes. However, the well-known immunomodulatory effects of dietary fatty acids [86] could be one of the underlying mechanisms that, in turn, could be linked to gut microbiota changes [87, 88]. Indeed, recently common food additives called emulsifiers have been found to promote colitis and metabolic syndrome in mice by altering gut microbiota [89]. Although further studies are needed to generalize and shed light into the underlying mechanisms that could explain the link between the intake of artificial food coloring and ADHD, we may speculate that theoretically changes on microbiota composition could be involved.

According to the results of a recent meta-analysis, omega-3 levels are reduced in children with ADHD and omega-3 dietary supplementation appears to provide modest although significant evidence of clinical efficacy for improving ADHD symptoms [90]. Omega-3 influences the levels of neurotrophins, molecules that increase neuronal growth and survival. Particularly, changes on the levels of BDNF have been reported to be associated with dietary omega-3 fatty acids intake [91]. A prospective study identified an association between a "Western" dietary pattern (high in refined sugar and animal fats) and ADHD onset in adolescents [92]. Western diets, rich in saturated fat and simple sugars, are known to be major contributors to gut dysbiosis. In contrast, rural or traditional diets rich in complex carbohydrates (fiber) are associated with increased proportions of beneficial bacterial species in the human gut microbiota. A major characteristic of the modern Western diet is the increase in the consumption of omega-6 PUFAs

relative to the consumption of the anti-inflammatory omega-3. A decreased dietary intake of omega-3 PUFAs has been associated with many inflammatory-related conditions including psychiatric disorders [93] whereas omega-3 supplementation has been shown to be protective against depression, dementia and age-related cognitive decline [94]. It is noteworthy that the proposed mechanisms by which omega-3 PUFAs may beneficially influence mental health are the regulation of BDNF and neurotransmitters levels as well as regulation of HPA axis activity, which have been linked to changes in behaviors; nevertheless, whether PUFA-induced gut microbiota changes could be involved in those effects remains to be determined.

Diets rich in polyphenols have been suggested to help maintain normal brain function in both large-scale epidemiological studies [95] and intervention studies [96]. In the context of ADHD, a polyphenolic extract from pine bark has been shown to reduce hyperactivity in ADHD children together with a decrease in catecholamine excretion and oxidative stress [97]. Although different mechanisms have been proposed to account for the positive effects of polyphenols in mental health, including their anti-oxidant and anti-inflammatory properties, an indirect effect via modulation of gut microbiota composition cannot be rule out. In fact, approximately 90% of dietary polyphenols are accumulated in the large intestine where they are broken down into less complex metabolites by gut microbiota [98]. It has been described that polyphenol metabolites modulate gut microbiota composition, favoring the growth of potentially beneficial bacteria such as *Bifidobacterium* spp. and reducing that of potentially pathogenic microorganisms in both animal and human studies [99, 100].

There is an increased prevalence of both constipation and fecal incontinence in children who suffer ADHD and this occurs independently of any pharmacotherapy [101]. These findings suggest that gut dysbiosis could be associated with the gastrointestinal dysfunctions observed in ADHD patients and could play a role in brain functioning and behavior in these cases. Increasing evidence also suggests that food allergies in children and adults are associated with behavioral problems and neuropsychiatric disorders, including ADHD, and dietary-based treatments in children with allergic disorders have shown to reduce ADHD-like behavior [102].

Of note, most of the aforementioned factors associated with both ADHD development and alterations in gut microbiota composition are also factors related to the development of many other diseases. Therefore, the combination of the effects of host genetics and microbiome together with those of environmental factors could be indispensable for explaining ADHD development and its different manifestations.

In a recent human study, the administration of a specific probiotic during the first 6 months of life seems to reduce the risk of ADHD development at 13 years of age, although differences in gut microbiota composition were no detected [103]. This finding, although encouraging, requires confirmation in well-powered studies. In addition, further studies are also needed to progress in the understanding of the possible role of intestinal dysbiosis in the risk of developing ADHD and clinical manifestation of the disease by applying high-throughput omics technologies. In addition, the role of the activity of gut microbiota in drug metabolism should also be investigated since this might partially explain the inter-individual variability observed in the efficacy and side effects of ADHD treatment.

Gut microbiota, oxidative stress and immune imbalance in ADHD

Based on the described current evidences, a new potential theory of immunopathogenesis for ADHD might be proposed. Nowadays, it is well recognized that under normal physiological circumstances there is a balance within the gut microbiota composition, known as eubiosis state, strongly associated with immune homeostasis. However, many environmental factors such as diet or even endogenous signals, caused by genetic or epigenetic factors, may disturb gut microbiota homeostasis leading to a microbial imbalance recognize as dysbiosis. This microbial imbalance is characterized by an increase of potentially inflammatory microbes and associated with an immune homeostasis breakdown linked to many immune mediated disorders. In turn, those microbiota alterations, by disrupting the intestinal permeability, may trigger migration of intestinal bacteria into the systemic circulation (microbial translocation) which might contribute to systemic inflammation [104–106]. Systemic inflammation and also other factors may contribute to the breakdown of the blood–brain barrier and, consequently, to neruroinflammatrion associated with different mental health problems such as ADHD. So far several studies have reported increased serum levels of pro-inflammatory cytokines such as IFN-g and IL-16 in ADHD patients [107]. Furthermore, currently it is well recognized that the human immune system and gut microbiota interact with each other in such a way that the microbiota strongly modulate the immune system and vice versa. Therefore, it is tempting to speculate that the compromised immune balance linked to ADHD might be triggered by alterations in the gut microbiota composition and also that the dysregulated immune profile, in turn, may lead to a more compromised gut microbiota balance. Gut microbiota composition also modulate oxidative stress [108, 109] which has also been reported to be significantly increased in ADHD patients [110–112]. Oxidative stress, known as the imbalance

between production of reactive oxygen species and their elimination by protective mechanisms such as antioxidants, may be contributing to the neuronal damage and the abnormal neurotransmission linked to ADHD. Therefore, it could hypothesize that both features, inflammation and oxidative stress, partly triggered by alterations in gut microbiota composition and associated with ADHD may be playing an important role in the etiopathogenesis of the disorder contributing to the development of ADHD symptoms by inducing neuroinflammation.

Conclusions and future perspectives

Nowadays we are beginning to understand the extent to which the gut microbiota influences brain function and behavior via the gut–brain axis, being this axis an appealing therapeutic target for treating developmental disorders such as ADHD, possibly without side effects. There is preliminary evidence indicating that specific diets or dietary components (including probiotics) may alter brain activity in regions of relevance to cognitive performance, behavior and specific ADHD symptoms and diet is well known to modify the gut microbiota. In addition, it has been reported mainly in preclinical studies but also in a few human studies that brain function and behavior are highly dependent on the gut microbiota composition and many evidences suggest that gut microbiota might be linked to the risk of developing ADHD and/or its manifestations. However, so far there is no a single specific study investigating the role of the gut microbiota in ADHD and thus, we strongly argue that the study of the role of the gut microbiota in ADHD is currently more than warranted. In addition, it would be interesting to examine whether or not some microbiome alterations associated with ADHD in humans are causally related to the disorder or its different manifestations in experimental models using a translational approach. Furthermore, it would be desirable to find out the exact altered routes of communication between the brain and the gut microbiota involved in ADHD to better understand the mechanistic basis of this disorder. These altogether could pave the way towards microbiota-targeted interventions that might improve the disease management.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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