Autism Spectrum Disorder and Gut Microbiota

Definition

Autism is a group of neurodevelopmental disorders, characterized by early onset difficulties in social communication and restricted, repetitive behaviors and interests. It is characterized by familial aggregation, suggesting that genetic factors play a role in disease development, in addition to developmentally early environmental factors. An intimate relationship between ASD and several medical comorbidities, such as sleep problems and many psychiatry-related comorbidities, i.e., attention-deficit/hyperactivity disorder (AD/HD), anxiety, mood problems, and disruptive behavior, was reported. Anyway, gastrointestinal comorbidities have a special role in their association with ASD. Indeed, since 1943, Kanner reported that ASD subjects showed severe feeding difficulties from their first days of life. Studies related to this association have crossed the entire path of evolution of knowledge on ASD. This association sustained a close relationship between ASD and gut microbiota.

1. Gut Microbiome Modification: Studies and Outcomes

A growing body of evidence indicates that altered gut microbiota negatively affects neurodevelopment and behavior, suggesting its potential implication in a number of neuropsychiatric disorders [1][2].

The idea of a possible involvement of gut microbiota in ASD was firstly postulated in 1998 by Bolte [3], who speculated that Clostridium tetani could induce autism. In 2000, a pilot study, published by Sandler et al., reported temporary improvements in both the behavioral and gastrointestinal symptoms in autistic children after six weeks of treatment with oral vancomycin [4]. The gradual regression of the symptomatology, following the discontinuation of the treatment, was explained by a later germination of Clostridium’s spores, which are resistant to antibiotics [1][3][6].

These early findings, coupled with the frequent occurrence of GI symptoms in ASD, have led numerous researchers to investigate the composition of the gut microbiota in autistic subjects, comparing it with that of neurotypical controls (NT).

Starting from those studies, the evidence of microbial dysbiosis in ASD has been growing, although controversial results have been observed among studies.

The most abundant phyla reported in the included studies are Firmicutes and Bacteroidetes, followed by Proteobacteria and Actinobacteria.

Firmicutes were found to be increased [7][8] or decreased [9][10] in autistic subjects, according to different studies. The same occurred for Bacteroidetes, with three studies describing higher levels in ASD [10][11][12] and two others reporting the opposite results [7][13].

A considerable enrichment has often been described for Actinobacteria [7][14][15] and Proteobacteria [7][12][15] in ASD. Plaza-Díaz et al. [15] also performed a subclassification in children with ASD by mental regression (AMR) and no mental regression (ANMR), showing that Proteobacteria was only augmented in AMR subjects.

As for the phyla, heterogeneous results have been observed at the genus level. Among Firmicutes, much focus has been given to Clostridium, which was found to be increased in autistic subjects compared to controls [10][14][15][16][17][18][19][20][21].

These spore-forming bacteria can release pro-inflammatory toxins and potentially toxic metabolites, as...
studies have reported in ASD neurotypical subjects. Several studies have previously described in gastrointestinal diseases, including sporadic diarrhea, food poisoning, and antibiotic-associated diarrhea. A positive correlation between clostridia and GI symptoms in ASD has also been described by Strati et al., who reported a significantly higher abundance of Clostridium cluster XVIII, as well as the opportunistic pathogens Escherichia/Shigella, in constipated autistic cases. However, further investigation is required to clarify their role in ASD and GI complications.

Some studies also reported higher levels of C. difficile in autistic subjects compared to NT ones. Nevertheless, a recent study showed that, although there was a higher percentage of C. difficile in autistic cases and their siblings compared to a group of unrelated controls, there was no statistically significant difference between the three groups.

Luna et al. reported a considerable increase in several mucosa-associated Clostridiales in ASD children with GI disorders, including Lachnoclostridium bolteae, which is in compliance with other studies. On the other hand, other Clostridiales, including Dorea formicigerans and Blautia luti, as well as Sutterella spp, were decreased.

Cao et al. observed an increased abundance of Desulfovibrio in ASD, which is in line with previous results. These bacteria could be relevant contributors to GI complications in ASD, as they produce LPS and hydrogen sulfide that can have cytotoxic effects on intestinal cells. There are still conflicting results about the alterations of the Bacteroides genus, which was found to be increased or decreased in ASD subjects in different studies. Their abundance strongly correlates with the fecal levels of propionic acid (PPA), since they are among the main producers of this metabolite. The high concentration of PPA has been related to behavioral disorders in a number of studies on rodents, butyric acid, another relevant short-chain fatty acid (SCFA), is known for its anti-inflammatory and protective properties. Indeed, it can protect the integrity of the intestinal epithelial barrier, strengthen mucosal immunity, and also modulate neurotransmitter gene expression. Furthermore, it has been reported that butyrate can restore blood–brain barrier permeability by inducing an increased expression of tight junction proteins, supporting its essential role in the physiological activities of the gut–brain axis.

Several studies reported significant alterations in the relevant abundance of butyrate producers in ASD subjects, such as various members of Lachnospiraceae and Ruminococcaceae families, whose levels have been found to be lower in ASD cases compared to controls.

Decreased levels of Bifidobacterium, which can have beneficial effects through its anti-inflammatory properties, have often been reported in ASD. Furthermore, Ahmed et al. discovered that the only significant difference between the gut microbiome of autistic children and that of their healthy siblings was the higher abundance of Bifidobacterium in the siblings’ group, supporting its protective role. However, it must be said that other studies reported the opposite trend between autistic and neurotypical subjects. Interestingly, higher levels of Lactobacillus, widely recognized as probiotics, have been reported in ASD, but, as for other bacteria, there is no consensus among the studies.

Several studies also described a decreased abundance of Prevotella, a commensal microorganism that
plays an important role in saccharides metabolism and the biosynthesis of vitamins \[27\] \[28\]; lower levels have also often been reported for Veillonella \[11\] \[13\] and Faecalibacterium \[8\] \[26\] \[29\]. Ding et al. also observed an association between the severity of symptoms and the relative abundance of Faecalibacterium strains, with the lowest levels in children with severe ASD compared to those with mild ASD and healthy controls. The opposite trend was described for unidentified Lachnospiraceae and Erysipelotrichaceae strains \[26\].

Another considerably decreased bacterial genus is Akkermansia, especially the Akkermansia muciniphila species, and, as they are crucial mucin degraders, their reduction may result in a relevant increase in gut permeability \[10\].

Even though most of these studies were focused on bacteria, a few of them also reported alterations in fungal components of the gut microbiota. At the phylum level, no statistically significant differences were detected. At the genus level, two studies reported a relevant increase in the abundance of Candida, especially in the Candida albicans species \[13\] \[27\]. The release of ammonia and toxins, as well as the reduced absorption of minerals and carbohydrates, due to the increased counts of Candida, may lead to autistic behavior \[27\] \[29\]. These fungi commonly colonize mucosal surfaces of the GI tract, where their growth is strictly regulated through competition with and suppression of the resident flora \[27\]. Indeed, gut bacteria and fungi live in a subtle balance and mutually influence each other. It has been observed that bacterial dysbiosis after antibiotic treatments can lead fungal commensals to bloom. As a consequence, the colonization of Candida albicans can interfere with the restoration of the healthy bacterial community, further contributing to dysbiosis \[27\] \[13\].

In contrast with previous results, a recent study reported higher levels of Candida albicans in controls compared to ASD subjects. They also detected an increase in Saccharomyces, potential human pathogens, and a lower abundance of Aspergillus in ASD. In particular, the highest abundance in autistic subjects was found in Saccharomyces cerevisiae, whose high levels have already been observed in schizophrenic patients. Among Aspergillus, the Aspergillus versicolor species, well known for its metabolites with anti-inflammatory activities, was significantly decreased in autistic subjects \[29\].

Overall, several studies reported an increase in the abundance of harmful bacteria and a decreased presence of beneficial ones, but observations on individual microbial taxa are often contradictory and, currently, it is not possible to describe a specific microbial signature of ASD.

These discrepancies may be attributed to several reasons, including the restricted number of participants and the considerable differences in sampling methods, analytical techniques, referred databases, and statistical methods among the studies. The aforementioned factors negatively impact the reliability of the comparison between studies, suggesting the need for standardized methods of analysis. Furthermore, the composition of the gut microbiota can be significantly affected by geographical, dietary, genetic, environmental, and cultural differences, which should be considered as additional confounding elements. For these reasons, all the results must be considered with caution.

## 2. Gut Microbial-Based Treatments

In the past two decades, the mechanisms underlying the bidirectional communication between the GI tract and the brain, through the so-called gut–brain axis, have been a subject of fast-growing interest. While the brain–gut interactions have been extensively investigated, the role of the gut microbiome as a key modulator of brain health and disease has only recently been addressed \[30\]. Although further studies are needed in order to fully elucidate its implications and signaling pathways within this context, it is clear that the gut microbiome can affect brain activities, both directly and indirectly, through a number of neural, endocrine and immune connections \[31\]. Ever since the influence of the gut microbiome on brain functions has been proved, many efforts exploring the impact of dysbiosis on neuropsychiatric disorders have been performed. Gnotobiology studies on germ-free (GF) animals demonstrated that the brain and behavior are significantly affected in the absence of a gut microbiome \[32\] \[33\] \[34\]. Furthermore, the
transplantation of an ASD microbiome into GF mice induced altered behaviors, including decreased sociability and repetitive behavioral patterns [35] [36], as well as alternative splicing of ASD-relevant genes, suggesting that a pathogenic microbiota may contribute to the genesis and development of the disease [35]. In light of the above, it is reasonable to speculate that targeting the gut microbiome may be a novel and safe therapeutic approach for ASD.

The most investigated approach is the administration of probiotics, sometimes combined with prebiotics. The International Scientific Association for Probiotics and Prebiotics (ISAPP) defines probiotics as “live microorganisms that, when administered in adequate amounts, confer a health benefit to the host” and prebiotics as substrates that are “selectively utilized by host microorganisms, conferring a health benefit” [37]. The use of probiotics in the management of a psychiatric disorder was first proposed by Logan and Katzman, who postulated that the administration of probiotics may be used as an adjuvant therapy in patients suffering from major depressive disorder [38]. In 2013, Dinan and colleagues used the term “psychobiotics” to describe a novel class of probiotics with potential therapeutic applications in treating psychiatric illnesses [39]. Even though the exact mechanisms by which these microorganisms act have not been clarified yet, a growing body of literature provides evidence of their beneficial effects on ASD. However, the different studies evaluated the effects of distinct probiotic mixtures.

A supplement formula based on three probiotic strains, including Lactobacillus acidophilus, Lactobacillus rhamnosus, and Bifidobacterium longum, was administered to a group of ASD-diagnosed children for three months. Significant improvements in both the GI and core symptoms of ASD were observed after the treatment, as well as a notable amelioration of gut microbiome composition, revealed by a substantial increase in Bifidobacteria and Lactobacilli [40]. De Simone Formulation (DSF), marketed as Visbiome® in the USA and Vivomixx® in the EU, is a probiotic supplement made up of eight probiotic strains, mostly Lactobacilli and Bifidobacteria, including Lactobacillus para-casei, Lactobacillus plantarum, Lactobacillus acidophilus, Lactobacillus delbrueckii subsp. Bulgaricus, Bifidobacterium longum, Bifidobacterium infantis, Bifidobacterium breve, and Streptococcus thermophilus. In a double-blind randomized controlled trial by Santocchi et al., DSF was orally administered to a group of ASD children at the posology of two packets/day for one month and one packet/day for the following five months. According to their findings, autism severity, as well as the levels of plasma and fecal inflammatory biomarkers, did not show any statistically significant difference after the treatment. Interestingly, the supplementation with DSF, compared with a placebo, provided different effects on ASD subjects with and without GI symptoms. Indeed, the children of the first subgroup experienced improvements in their GI complaints, sensory profiles, and adaptive functioning after the treatment [41]. These results are in line with a previous pilot study by Arnold et al., who described an amelioration in GI symptoms in a cohort of ASD children treated with DSF [42]. On the other hand, children without GI symptoms showed significant modifications in their core symptoms of ASD, revealed by a decline in ADOS-CSS scores (total autism diagnostic observation schedule—calibrated severity score), compared with a placebo. These observations suggest that probiotics could positively affect the behavioral symptoms of ASD independently from the intermediation of their effects on GI symptoms. Furthermore, children with and without GI symptoms may potentially represent distinct populations in which probiotics could act through different mechanisms, probably due to different microbiota targets [41].

References


**Keywords**

autism spectrum disorder; gut microbiota; gut-brain axis

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