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Review Article

The Intricate Interaction between Enteric Microbiota and Brain: Principles and Clinical Implications

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Abstract

The intestinal microbiome consists of a bacterial community that lies largely in the distal bowel where almost 100 trillion of microorganisms are present.The gut and the brain are strictly interconnected by a physiological communication system known as the gut-brain axis, involving endocrine, nutritional and immunologic mechanisms. The gut-brain axis plays a crucial role in the modulation of several brain areas and alterations in its function are often associated with psychiatric conditions.The current review, besides providing an overview of the microbiome composition and its diet-based changes, will focus on the recent advances in the understanding of how the gut-brain axis influences brain functions.

Keywords: Brain Health;Diet; Gut Micro Biota;Lifestyle;Vagus Nerve

Composition and Diversity of the Intestinal Micro Biota

In the human body a vast number of organisms, including bacteria, archaea, viruses and unicellular eukaryotes live and coexist, and all together have been referred to as the microbiota, commensal microflora, or normal flora [1]. The overall human microbiota that habits our body are present in virtually every surface exposed to the external environment and is estimated to contain as many as 1014 bacterial cells, 10-fold greater than the number of human cells [2-4]. The most heavily colonized organ is the gastrointestinal (GI) tract, rich in molecules that are important substrates and nutrients for microbes, whereas the colon alone is estimated to be colonized by over 70% of the entire human microbial community [2-4]. The intestinal microbiome represents a complex endocrine organ and, due to its complexity of functions, it is often referred to as "a forgotten organ" [5].

Gut microbiota in adults is mainly composed of strict anaerobes, which largely dominate the facultative anaerobes and the aerobes [6]. In particular, although the presence of more than 50 bacterial phyla has been described to date in the human gut, the microbiota population is profoundly dominated by only 2 of them, accounting for approximately 60%-90%: the *Bacteroidetes* and the *Firmicutes*, whereas *Proteobacteria, Verrucomicrobia, Actinobacteria*, *Fusobacteria* and *Cyanobacteria* are present in minor proportions [2,7]. The estimated number of bacterial species present in the mammalian gut varies widely between different studies, although it is generally accepted that adults harbor more than 1,000 microbial species [8,9]. A recent analysis involving multiple subjects has suggested that, overall, the human gut microbiota is

composed of more than 35,000 bacterial species [10]. These bacterial species have variable distribution along the length of the GI tract, with cell numbers varying from 10 to 103 bacteria per gram of contents in the stomach and duodenum, increasing to between 104 and 107 bacteria per gram in the jejunum and ileum (small intestine), and reaching to between 1011 and 1012 bacteria per gram in the colon (large intestine) [5,11]. Moreover, the microbial composition and the amount of different bacterial species vary between the different sites in the small intestine and colon [10]. Comparing healthy individuals' biopsy samples from both sites, the small intestine was found to be enriched with certain members of the Bacillus class of Firmicutes phyla and Actinobacteria, while members of the Bacteroidetes phylum and the Lachnospiraceae subgroup of Firmicutes were more prevalent in the colonic tract [10].In addition to the longitudinal variation of the intestinal microbiota observed along the length of the GI tract, latitudinal variations also exist, involving the microbial composition in transverse section of the intestine [12]. In fact, it has been observed that the microbial composition in the intestinal lumen differs significantly from that in the immediate proximity of the epithelium, with many lumen-colonizing species being unable to access the intestinal epithelial layer [12]. As an example, the genera *Bacteroides*, *Bifidobacterium, Streptococcus, Enterococcus, Clostridium, Lactobacillus* and *Ruminococcusare* present in the microbial flora of the lumen, whereas only Clostridium, *Lactobacillus*, and *Enterococcuscan* be detected in the mucus layer and epithelial crypts of the small intestine [12].

The composition of the human gut microbiota has been observed to change substantially during the different epochs of life, in parallel to diet changes over the years [13,14]. Microbial colonization of the human gut begins at birth, when the neonate intestine is believed to be sterile or contains a very low level of microbes [15]. The human gut is quickly colonized during and after delivery, when the neonate passes through the birth canal. Thus, the intestinal microbiota of infants and the vaginal microbiota of their mothers show similarities [16], whereas differences in the microbial composition have been described between infants delivered through cesarean section compared to those vaginally delivered [17]. During the first year of life, the gut microbial composition is relatively simple althoughit varies widely between different individuals [16,18]. Afterward, the intestinal microbiota community of children starts to be similar to that of young adults and stabilizes [16,18]. It is believed that during the early stages of life both the initial colonization and the diet play a crucial role in shaping the adult intestinal microbiota [19].

Besides the mother's microbiota composition, gut microbial diversity is also influenced by different internal and external factors. Among the external factors, the environmental microbial load, diet and feeding habits and drug therapy appear to significantly affect microbial composition. With regard of the drug therapy, for example, the use of broad-spectrum antibiotics, commonly prescribed in clinical practices, has been shown to reduce the gut microbiota diversity and delay the colonization by some probiotic strains, such as *Lactobacillus sp.* [20]. The major internal factors influencing microbial composition include microbial interactions, environmental temperature, intestinal acidity, physiological peristalsis, bile acids, host secretions and immune responses, bacterial mucosal receptors, and the host's genetic factors, that likely work indirectly by acting on the general host metabolism [11,18]. However, despite the enormous amount of different factors that can influence the gut microbial composition, the microbial community in the human gut is fairly stable at the phylum level [11]. As stated above, the *Bacteroidetes* and *Firmicutes* are the major phyla found and are conserved in all individuals, although the relative proportions of these phyla can vary. Additionally, within phyla, at the level of genera and species, the human gut composition is also considerably different between individuals [21,22].

A conceivable explanation for the microbiota diversity, although not experimentally proved, is likely the functional redundancy within microbial groups of the gut microbiota; different bacterial species within the major phyla might be able to carry out a functional process at the same rate, ensuring the maintenance of proper specific functions within the gut [9,11]. From birth to weaning, maternal and neonatal dietsare also critical for shaping the gut microbiota [13,23]. Breast milk is rich in a wide variety of important prebiotics, such as the human milk oligosaccharides,impactingboth on growth and body mass regulation, as well as nucleotides, immunoglobulins, cytokines and short-chain fatty acids (SCFAs) [23,24]. Oligosaccharides are fermented by *Bifidobacteria* that, along with lactic acid bacteria, represent the most prevalent bacterial species in the gut of breastfed infants and are important for the production of SCFAs and for the maintenance of gut homeostasis [24,25]. Conversely, the microbiota of formula-fed infants typically shows a higher diversity including Bacteroidetes, Clostridia, and *Bifidobacteria,* with an overall increase in facultative anaerobic bacteria associated with pathogenesis, such as *Staphylococcus*, Enterobacteriaceae, and *Streptococcus* [23,26].

The infant's gut microbiota changes are strongly correlated with a shift from breastmilk/formula diet to a solid diet, causing an increase in the Bacteroidetes to Firmicutes ratio, along with a reduction in *Proteobacteria* and *Bifidobacteriaand* an overall increment in functional genes characteristic of an adult microbiota [18,27].A drastic variation in the compositionof the intestinal microbiota has been observed comparing young healthy adults to elderly individuals, due to age-related factors associated with physiological and morphological changes in the gut [28,29]. In elderly people, a decrease of intestinal microbiota diversity and composition has been observed, associated with a reduction in the

levels of bacterial species such as *Bifidobacteria* and *Bacteroides*, and a concomitant increase in the proportion of *Ruminococcus, Clostridium, Enterobacteriaceae*, and *Lactobacillus* [8,23].

Microbiota, Function and Host Metabolism

The gut microbiota encode alargely greater number of genes than its human host.Therefore the microbial community exerts and is involved in a variety ofspecificmetabolic functions and physiological processes. For example, bacterial cells in the gut areable to protect the host from pathogens, synthesize a variety of vitamins and amino acids, allow biotransformation of bile acids, store host fat, and regulate brain physiology and behavior [30-32]. Additionally, many intestinal bacteria produce antimicrobial substances, known as bacteriocins, and compete for nutrients in their immediate surroundings and for sites of attachment in the intestine lining, thereby preventing colonization by pathogens. This action is known as the barrier or competitive-exclusion effect[33].Moreover, intestinal bacteria can produce a variety of neurotransmitters such as γ-aminobutyric acid (GABA), serotonin, melatonin, catecholamines and histamine, as well as gasses, such as hydrogen and ammonia, which areinvolved in the communication between various components of the microbiota and areessential for the functioning of the nervous, neuroendocrine and immune systems[34].

A main function of the intestinal bacteria is to provide vital biochemical pathways for digestive processes, such as those involved in the metabolism of carbohydrates, resulting in the recovery of energy and substrates absorbed by the host and also representing a source of energy and nutrients for bacterial growth and proliferation [33].Bacteroidetes phyla mainly produce the SCFAs acetate and propionate, whereas butyrate is predominately synthesized by Firmicutes. Through the production of SCFAs, mainly derived from the fermentation of undigested carbohydrates in the colon and large intestine, the gut microbiota is able to regulate several host physiology processes and immune functions via epigenetic mechanisms, such as the regulation of the functions of regulatory T cells, the regulation of the metabolism of lipid, glucose, and cholesterol in various tissues, and the control on the release of several satiety hormones [23].

The intestinal epithelium represents the main interface between the immune system and the external environment. Interactions between gut microbiota and their metabolites with the immune system promote the enhancement of an immune response of the host in the human gut and at distant organs. Thus, the state of the gut microbiota directly affects the innate and acquired immune system [35].The interactions between the microbiome and mucosal cells are regulated by the production of different cytokines and chemokines, both inflammatory (interleukin-8 and interleukin-1) and anti-inflammatory (interleukin-10 and transforming growth factor beta) [3].Since the bacterial gut flora is often found at sites enriched with immune cells including epithelial cells, mucus, immunoglobulin A, and antimicrobial peptides, the interactions between all these components seem to play an important role in the regulation of a homeostasisbetween microbiota and the host gut, by limiting the contact between the microbiota and host tissue, preventing microbial translocation, and regulating the gut microbiota composition [36]. In addition, the gut microbiota may activate a peripheral immune response by releasing certain molecules, such as LipoPolysaccharides (LPS) and peptidoglycans, which can be translocated from the gut through the intestinal mucosal barrier, acting as potent promoters of the innate immune system. Therefore, the intestinal microbiota composition influences barrier integrity: an increase in gut permeability and translocation of bacteria and their products inside the internal tissues (a mechanism referred to as the permeable intestine or “leaky gut” [37, 38] has been implicated in several pathophysiological conditions, such as obesity, several human chronic diseases and psychosomatic symptoms [34].

Role of Diet in Microbiota Composition

Changes in diet composition, even within a short duration, have a drastically direct impact on the gut microbiota in adult individuals [39]. It has been reported that a high-fat diet, as is the case of the so-called Western diet, causes a change in the Bacteroides to *Firmicutes* ratio with a significant reductions in Bifidobacteria, Bacteroides, and butyrate-producing bacteria [40-42]. In addition, an increasein the relative abundance of Collinsella, bacteria associated with Obesity has been observedin humans with Western diet [42].

On the other hand, the Mediterranean diet - rich in fruits, vegetables, cereals, and legumes, with low consumption of meat - has been found to be associated with an increase in Bacteroides and Clostridium phyla and decrease in Proteobacteria and *Bacillaceae* [43]. These changes in the gut microbiota composition associated with the Mediterranean diet have been linkedto anti-inflammatory effects and, consequently, with a significant reduction in mortality and in the incidence of several chronic diseases, such as cancer, autoimmune and neurodegenerative diseases [44]. Moreover, the Mediterranean diet causes a significant increase in SCFAs that are critical for the maintenanceof the intestinal barrier [45].

Carbohydrates, proteins, bile acids, fatty acids, vitamins and polyphenols likewisecan affect the microbiota composition. Carbohydrates are metabolized by the gut microbiota and are then absorbed in the intestine as simple sugars. Carbohydrate fermentation produces highly-efficient energy with production of important metabolites, such as SCFAs[46].Indigestible carbohydrates, such as cellulose and hemicelluloses present in plants, are often metab-

olized in the distal part of the colon, mostly by Bacteroides or Ruminococcus species, and, therefore, abundance in the Bacteroides species has been reported in individuals that use rural diets[47]. Dietary regiments rich in fibers belonging to a group of carbohydrates or carbohydrate-containing compounds not easily digested, have been associated with a high diversity of the gut microbiota, by elevating the relative abundance of *Bifidobacteria* and *Lactobacilli* in the human intestine, essentials for the maintenance of a healthy microbiota [48].Changes in the composition of dietary carbohydrates are also implicated in affecting the microbiota composition. Of note, a recent study in healthy individuals showed that a short-term gluten-free diet determines a significant reduction in the Veillonellaceae family (class Clostridia), pro-inflammatory bacteria involved in lactate fermentation [49].

Protein-rich diet is often associated with an increase in Bacteroides levels in the gut, because Bacteroidesareinvolved in the initial proteolysis [50]. In addition, protein-rich dietary consumption has been found to result in an abundance of Atopodium, Clostridium, Prevotella, Veillonellasps, and the bile-tolerant bacteria Alistipes and Bilophila, with a reduction in Firmicutes[51]. Moreover, protein-rich animal-based diet in mice results in a significant increase in Bilophilawadsworthia, a gut-specific bacterium associated with colitis and a variety of inflammatory chronic gastrointestinal diseases [52].

Intestinal flora is also important for bile acid synthesis, and intestinal *Bacteroides sp*. in bile acid deconjugationhas been reported to promote the protection of the colonic epithelium cells from genotoxic agents [53].Omega 3 and omega 6 are polyunsaturated fatty acids (PUFAs), biosynthetic derivatives of alfalinoleicand linoleic acids. They are found mainly in fish and in some plant oils, with proved positive effects on neuroprotection and on brain function, metabolism, and behavior [54]. PUFAs, especially omega 3, have been investigated for their crucial role in regulating the microbial composition and metabolism during early-life stress [55]. Importantly, most of the beneficial anaerobic bacteria including *Roseburia, Bifidobacteria,* and *Lactobacillus sp.* are widely found in the distal end of the gut, a preferred site for PUFA metabolism from linoleic acid [56].

The intestinal microbiota also appears to be associated with the synthesis of a variety of vitamins, thus enriching the immune system and the microbiota diversity [57]. Most of the microbial-produced vitamins are absorbed in the colon, while most of the dietary-derived vitamins are absorbed in the proximal part of the small intestine [58]. In germ-free mice, vitamin A deficiency has been linkedto a loss of gut T-helper TH17 cells in the small intestine, and to a significant reduction in the gut bacteria belonging to *Clostridiaceae* [59]. Similarly, high doses of vitamin D3 have been correlated with changes in the gut microbiota composition, with reductions in gamma *Proteobacteria* in the upper GI tract [60]. Indeed, deficits of vitamin D are associated with various proliferative, neuropsychiatric, inflammatory and metabolic disorders [23]. In addition, the intestinal microbiota also plays a role in the synthesis of biotin and folate, vitamins closely involved in the epigenetic regulation of colonic epithelial proliferation, in DNA repair, and in various anabolic pathways, such as synthesis of nucleotides, vitamins, and some amino acids [23].

Polyphenols are a heterogeneous group of compounds characterized by hydroxylated phenyl moieties, found in grapes, apple, pear, cherries, berries, tea, coffee, red wine, dry legumes, cereals and chocolate [61]. Small portions of polyphenols are metabolized in the small intestine, but the majorities are fermented in the large intestine by some intestinal bacterial species including *Bifidobacterium sp., Lactobacillus sp., Bacteroidetes sp., Eubacterium sp.* and *Escherichia coli*. Polyphenols are known to induce numerous beneficial effects associated with inflammation, neuroprotection, antioxidation, cardiovascular diseases, cerebral ischemia and metabolic disorders [61,62].

A growing body of evidence suggests that the microbiota may be responsible for some of the beneficial effects of polyphenols, and an association between polyphenols and an increment in the gut microbiota composition diversity has been suggested [62]. For example, the polyphenol catechin, found in green tea, has been shown to markedly inhibit the growth of *Clostridium sp*., whereas the growth of *Bifidobacterium sp.* and *Lactobacillus sp.* remains unaffected and, in another recent study, catechin inhibited "in vitro" the fecal growth of *Bacteroidetes* and *Firmicutes* [63,64]. Moreover, resveratrol, commonly found in grape, has been found to promote fecal numbers of *Bifidobacterium sp.* and *Lactobacillus* in a murine model, and, similarly, consumption of red wine containing resveratrol showed significant increases in *Enterococcus, Prevotella, Bacteroides, Bifidobacterium, Bacteroidesuniformis,Blautiacoccoides*, and *Eggerthellalenta*, where as *Lactobacillus* numbers remained unaffected [65,66].

Gut Brain-Axis

The gut-brain axis acts as an integrative physiological system merging nutritional, endocrine, immunologic, efferent, and afferent neuronal signals between the GI system and the brain.The evidence that the microbiome can impact on brain functions stems from clinical observations. For example, rifaximin, a semisynthetic rifamycin-based antibiotic that reduces intestinal production and absorption of ammonia by altering microbiota composition, has been shown to be effective in improving behavioral, mental, and intellectual abnormalities in patients with hepatic encephalopathy [67]. Other evidence arises from the observation that several psychiatric disorders frequently coexisting with common gastro-

intestinal conditions, such as irritable bowel syndrome, are also associated with disturbances of the intestinal microbiota [68].Various experimental studies carried out on animal models of psychiatric disorders, including those affecting early brain development, and neurological disorders such as multiple sclerosis,have further extended the notion that the microbiome interacts with the brain [69-71].

Thus, the microbiome and its regulating factors are rapidly becoming an important field of research, and nutritional interventions across the lifespan play a key role in assuring a physiological brain health. The complex network of communication between the gut microbiome and the brain is mainly mediated through the Autonomic Nervous System (ANS), the enteric nervous system, the immune system, and the bacterial metabolites [72]. Here, we report recent advances in our understanding of how the intestinal microbiota communicates with the brain via the gut-brain axis to influence brain development and behavior.

ANS Mediation

The enteric nervous system, or second brain, embedded in the gut wall along the GI tract, is a rather autonomous part of the ANS, and itis further innervatedby primary visceral afferent nerve fibers from both the sympathetic and parasympathetic branches of the ANS [73]. After ingestion of food or drink, the nutrients in the GI tract initiate complex neuronal and hormonal responses, informing the brain of the ongoing change in the nutritional status (FiguFigure 1:The gut-brain axis.

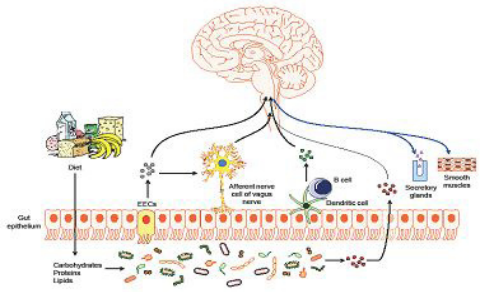

Figure 1: The gut-brain axis.

The brain and the gut are strongly bi-directionally interconnected. After food ingestion, the nutrients in the GI tract trigger complex neural and hormonal responses informing the brain of the change in the nutritional status. The connectivity between gut and brain is mediated by neuronal, immunological, endocrine and metabolic pathways. The vagus nerve is the major nerve for mediating the effects of gut microbiota on different neurophysiological function: the afferent fibers project from the gut to the subcortical and cortical areas of the brain, meanwhile effector fibers project to the smooth muscles and secretory glands of the gut. The EECs, located in gut epithelium, release signaling molecules or hormones that act directly on the receptors located along the afferent fibers of the vagus nerve or reach the brain through the bloodstream. The gut microbiota can both induce the immunitary system to produce an immune modulatory response and release neurotransmitters and hormones that reach the brain by the circulatory system.

Although the enteric nervous system can function on its own, stimulation by the ANS parasympathetic and sympathetic branches can modulate GI function including motility, secretion and absorption. The afferent fibers project information from the gut to the subcortical and cortical centers of the brain including the cerebral cortex, cingulate, and insular regions, whereas effector fibers project to the smooth muscles and secretory glands of the gut (Figure 1)[74]. This bidirectional communication helps to maintain a proper GI homeostasis, and cognitive functions.The vagus nerve is themajor nerve of the parasympathetic system of the ANS and is crucial for mediating the effects of gut microbiota on different neurophysiological functions [72].For example, experimental observations by Bravo and co-workers in 2011 demonstrated that the probiotic Lactobacillus rhamnosus is able to alter the mRNA expression of GABAreceptorsin cortical brain areas,andsimilar alterations have been involved in the pathogenesis of anxiety and depression [75]. Interestingly, the same Authors showed that neurochemical and behavioral effects were absent in vagotomized mice, identifying the vagus nerve as a major modulatory constitutive communication pathway between the bacteria exposed to the gut and the brain.Similarly, it was shown that the ability of the probiotic *Bifidobacterium* to normalize anxiety-like behavior is dependent on the vagus nerve integrity [76].Together, these findings highlight the important role of bacteria in the bidirectional communication of the gut-brain axis and suggest that certain organisms may prove to be useful therapeutic adjuncts in stress-related disorders such as anxiety and depression.

Enteroendocrine Cells

The vagus nerve does not project directly into the gut lumen, butits activation is partly dependent on the secretion of biological signals produced by specialized endocrine cells (comprising approximately 1% of the GI tract epithelial cells)that are capable of sensing luminal content and of producing and releasing signaling molecules.Thus, these enteroendrocrine cells (EECs) elaborate informative molecules which are then transmitted to the brain by both the blood circulation and the vagus nerve,making them critical foranormal bidirectional gut-brain communication. Importantly, gut microbiome and EECs are in direct contact along the GI tract, and this colocalization permits a strong mutual interaction allowing for the commensal bacterial to stimulate EECs in order to secrete various gut peptides. Moreover, the nutrients and food components in the gut act on proper receptors, mostly located on EECs[77,78]; collectively, these cellsfrom our largest endocrine

organ [73].Approximately 12 major EECtypes have been identified, altogether secreting more than twenty hormones. The hormones released by EECs can act on vagusnerve terminals, immune cells and other cells, or organs at remote sites including pancreatic islets.

The effects exerted through nutrient receptors on EECsinclude changes in food intake, changes in gastric emptying and intestinal transit, release of digestive enzymes, induction of nutrient transporters and digestive enzymes, an increase in intestinal barrier function, pancreatic insulin secretion and modulation of immune responses.These effects are mainly mediated by the vagus nerve, being the major constituent of a neural reflex mechanism involved in the control of innate immune responsesand inflammation during pathogen invasion [79-81],beyond the regulation of metabolic homeostasis, GI motility and secretion and regulation of both the endocrine and exocrine pancreatic secretion [73].Various experimental observations demonstrated the role of the vagus nerve in the peptide hormone function. For instance,Koda and coworkers demonstrated that vagotomy abolished the function of the gut peptide $PYY_{3-36}$and vagotomized mice displayed a clear hypoPhagic phenotype [82].This peptide, produced by gut EECs, is highly associated with reduction in food consumption[83].

Immune System Mediation

It is nowwidely recognized that the interaction with commensal microflora, present in the GI tract, are crucial for the proper function of the mammalian immune system [84].In fact, the microbiome isoften found at sites enriched with immune cells, playing an important role in the homeostatic relationship between the microbiota and the host mucus, immunoglobulin A, and antimicrobial peptides [85]. Several important effects of the microbiota on the host immune system have been determined by studies on germ-free animals. These animals are characterized by serious alteration in the development of gut-associated lymphoid tissues [84,86] and in antibody production, and have fewer and smaller Peyer's patches and mesenteric lymph nodes when compared with animals housed under specific pathogen-free conditions. These alterations in inducible structures are rescued following the introduction of gut bacteria, indicating a crosstalk between bacteria and the host immune system.The immune system is not only involved in maintaining homeostasis between the gut microbiota and the gut, but it may also act as an intermediary between the gut microbiota and the brain [87].The gut microbiota may mediate an immune response by releasing certain molecules, which are potent promoters of the innate immune system. For example, peripheral administration ofLPS or interleukin-1β leads to an activation of the vagus nerve, as shown by an increase of neuron electrical activity and c-Fos expression [88,89].

To the evidence that interleukin-1β activates central neuronal circuitries originating in the nucleus of the solitary tract (NTS),Ek and collaborators [90] added the functional evidence that circulating interleukin-1β stimulates vagal sensory activity via prostaglandin-dependent mechanisms, as the effect of interleukin-1β administration was attenuated in animals pre-treated with the cyclooxygenase inhibitor, indomethacin. Additionally, preclinical and clinical studies have shown that peripheral immune activation following LPS administration can lead to behavioral alterations[91,92]. Interestingly, such mental deficitsare significantly attenuated in vagotomised animals [88], suggesting that the behavioral alterationsare dependent on the magnitude of the immune activation. In addition to behavioral modulation, the microbiome has recently been implicated in the shaping of the brain's resident immune cells, the microglia. In fact, a substantial contribution of the host microbiota to microglia homeostasis has been reported [93]. The Authors observed that germ-free mice display defects in microglia with altered cell proportions and an immature phenotype, leading to impaired innate immune responses. Notably, microglia impairment can be rescued by complex microbiota, providing more evidence for the link between microbiota and brain health.

Microbiome and Brain Health: Clinical Implications

The experimental evidence that the microbiome can influence brain function has aroused great interest towards the link between microbiome dysfunction and human neuropsychiatric conditions. For instance, epidemiological studies report that GI distress is a common comorbidity in autism patients [94], and correlates well with symptom severity [95]. Moreover, a study reveals a higher prevalence of inflammatory bowel disease in autism patients when compared to controls [96]. On the basis of these epidemiological studies, preclinical investigations performed on mouse models demonstrated a crucial role of microbiome alterations in autism-like defects in offspring. Similarly, Hsiao and collaborators [97], using a maternal immune activation model (MIA; strongly linked to the development of neurochemical and behavioral abnormalities in offspring, [98]demonstrated that MIA mouse offspring displayed GI barrier, microbiota alterations and an abnormal intestinal cytokine profile characterized by high levels of the inflammatory marker interleukin-6, in addition to autism-like neurodevelopmental features. Notably, oral treatment of MIA offspring with the human commensalBacteroidesfragilisrescued gut permeability, and ameliorated behavioral social defects.More recently it has been reported that maternal high-fat diet causes gut microbiota dysbiosis in mouse offspring that additionally show a reduction in the number of oxytocin-immunoreactive neurons in the hypothalamus and social deficits. Interestingly, both social defects and microbiome dysbiosiswere prevented when the offspring were co-

housed with offspring of mothers following a regular diet [99]. The notion that the gut microbiota is also implicated in stress-related mood disorders, such as depression, has been recently suggested by the change in the composition of commensal bacteria observed in patients suffering from major depression [100]. In fact, the Authors found that the gut microbiotic composition of patients was characterized by significant changes in the relative abundance of Firmicutes, Actinobacteria and Bacteroidetes. Additionally, the Authors showed that the transplantation of dysbiotic stool from patients in germ-free animals resulted in depression-like behaviors, when compared with the same germ-free mice transplanted with stool from healthy individuals.

Conclusions and Future Perspectives

Here,we have reported only a small fraction of the published data on the relationship between the microbiome and brain health and on the role of diet in the shaping of the gut bacteria composition. Nevertheless, we strongly believe that further studies are neededin order to better characterize the molecular mechanisms by which the gut microbiome or the products of the microbiome-host interactionsare able to alter brain functions and thus drive brain pathology. It is clear from this summary that thorough clinical investigations are needed in order to unlock the therapeutic potential of diet for different neuropsychiatric conditions and we are confident that the use of probiotics will be further explored as adjuvant therapy inthe standard care inseveral mental illnesses in the near future.

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