Microbiota/Microbiome and the Gut–Brain Axis

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The human gut microbiota, mainly consisting of Proteobacterias, Firmicutes, Actinobacteria and Bacteroidetes, changes during the course of life, as it is constantly influenced by several individual factors, such as the type of birth, infections, therapies, diet, smoking, physical activity, stressful events, environmental factors and medical diseases. It is also worth highlighting that the brain's development, depending on pre- and post-natal genetic and environmental factors, occurs in parallel with the constitution of the microbiota. A newborn's microbiota has a low density but, as the individual grows, it is enriched with certain microorganisms, becoming increasingly capable of activating signals and metabolic pathways that modulate neuronal function.

microbiota gut–brain axis central nervous system immune system autism spectrum disorders mood disorders obsessive-compulsive disorder schizophrenia novel psychotropic drugs neuropsychiatric disorders

1. Introduction

The terms "microbiota" and microbiome refer, respectively, to the collection of bacteria, viruses and fungi colonising different parts of the body, and to the complete genetic material encoded by the microbiota [1][2][3]. The gut microbiota, i.e., the commensal microorganisms within the gut, performs essential tasks for the normal functioning of the organism, such as the fermentation and digestion of carbohydrates, development of lymphoid tissues associated with the mucous membranes, production of vitamins, prevention of colonisation by pathogenic microorganisms and stimulation of the immune system [2][4][5][6]. The bacterial cells forming intestinal microbiota outnumber human cells by 10 times and encode for a gene set that is 150 times larger than the human one [1]. The human gut microbiota, mainly consisting of Proteobacterias, Firmicutes, Actinobacteria and Bacteroidetes, changes during the course of life, as it is constantly influenced by several individual factors, such as the type of birth, infections, therapies, diet, smoking, physical activity, stressful events, environmental factors and medical diseases [7][8][9]. It is also worth highlighting that the brain's development, depending on pre- and post-natal genetic and environmental factors, occurs in parallel with the constitution of the microbiota. A newborn's microbiota has a low density but, as the individual grows, it is enriched with certain microorganisms, becoming increasingly capable of activating signals and metabolic pathways that modulate neuronal function [10][11][12][13].

The immune system appears to be at the heart of the gut–microbiota–brain relationship. Indeed, an altered composition of the gut microbiota might compromise the epithelial intestinal integrity and lead to a defective defence against pathogenic microorganisms, with consequent inflammatory reactions and, ultimately, neuro-

inflammation [14]. Moreover, dysbiosis causes an increase in the amount of short-chain fatty acids (SCFAs), such as acetate, propionate and butyrate, that might activate microglia cells, i.e., the immune cells of the CNS, leading to an increase in cytokines that may eventually alter brain connections and the blood–brain barrier (BBB) [15][16]. Interestingly, microbial-induced BBB dysfunction is hypothesised to play a causative role in mood and anxiety disorders, SZ, autism spectrum disorders (ASDs) and neurodegenerative diseases [17]. A role of the gut–brain axis in the development of CNS tumours was also proposed [18]. Finally, a growing number of findings suggest that the microbiota might modulate neuronal maturation and myelination processes in brain areas that are responsible for the control of emotions, executive functions and working memory, which are impaired in SZ, MDs and ASDs [19][20][21].

Given the available evidence, it is plausible that a better understanding of the influence exerted by intestinal flora on the CNS and the role of the gut microbiota in the onset and maintenance of psychiatric disorders might lead to producing novel treatments, including probiotics, personalised lifestyles, faecal microbiota transplantation (FMT) and specific diets [22].

Therefore, the aim of this paper was to review and comment on the current literature on the role of the intestinal microbiota and gut–brain axis in some common neuropsychiatric conditions.

2. CNS and Microbiota: The Gut–Brain Axis

The large number of novel studies on the relationships between microbiota and the CNS has led to the recognition of the gut–brain axis, that is to say, the bidirectional connection occurring between the gut microbiota and the brain through hormonal, metabolic, immunological and neural signalling, with the latter involving central, autonomic and enteric nervous systems [6][23][24][25]. This mutual connection seems to reflect a reciprocal influence: the diversity in microbiota composition affects brain development and behaviours, and vice versa [25].

Interestingly, brain changes that are promoted by microbiota might occur through the regulation of gene expression and neuronal transcription [26][27]. A murine model study demonstrated the upregulation of myelin-related genes in GF mice, specifically in the prefrontal cortex (PFC), leading to hypermyelinated axons. Furthermore, the subsequent colonisation of these animals (the so-called exGF) resulted in a reverted modulation [27]. Gene expression regulation that was driven by intestinal microbiota also led to the modulation of neuro-inflammation, production of insulin-like growth factor-1 (IGF-1) and changes in multiple neurotransmitter (serotonin (5-hydroxytryptamine, 5-HT), dopamine, glutamate and gamma-aminobutyric acid (GABA)) pathways, transporters and ion channels [26]. Focusing on neurotransmitters, male GF mice show increased 5-HT and 5-hydroxyindoleacetic acid (5-HIAA, the main 5-HT metabolite) in the hippocampus [28], while Bifidobacterium infantis administration in rats increased tryptophan, the 5-HT precursor [29]. As already mentioned, the effects of gut microbiota on neurotransmission extend beyond 5-HT. Non-pathogenic bacteria, such as Lactobacillus rhamnosus, modulate GABAergic transmission in mice, with beneficial effects on anxiety and depression [30], and GABA production by cultured intestinal strains of Lactobacillus and Bifidobacterium was observed [31]. Nonetheless, regarding the relationship between brain and GI tract, it is worth noting that about 90% of 5-HT is synthesised in

the gut, where it modulates GI motility, and then is sequestered by platelets and transported to various body sites, acting as a pleiotropic hormone [32][33]. Indeed, the intestinal synthesis of 5-HT seems to be positively influenced by microbiota, consequently increasing 5-HT in the GI mucosa and lumen, platelets, blood and brain. As such, microbiota influence peripheral and central 5-HT concentrations [33].

Furthermore, the links between the brain and gut also play a role in the immune response. An example of this link is provided by microglia. As the resident macrophages of CNS, microglia are involved in the immune surveillance of the CNS itself [34], and as such, possibly in different brain disorders [35][36]. Microglia maturation, activation and function are affected by microbiota composition. According to some authors, microglia changes are driven by gut eradication, re-colonisation and variations in microbiota complexity. Interestingly, GF mice share defective microglia and impaired innate immunity [35].

It should be noted that the GI tract represents the largest immune organ, as well as the largest surface of contact with external agents [37]; therefore, it was hypothesised that alterations of intestinal flora, through regulatory T cells (Treg) abnormalities, might be involved in the epidemic of allergic, inflammatory and autoimmune diseases and also in psychiatric disorders [38][39][40][41][42][43][44][45].

3. Microbiota and Psychiatric Disorders

Indeed, the interactions between the host and its microbiota seem to be able to produce significant changes in brain networks, thus influencing behaviours and neuropsychiatric disorders [46].

Regarding the relationship between microbiota and SZ, research is still in its infancy. As mentioned above, animal studies underlined the role of microbiota in the postnatal development and maturation of neuronal, immune and endocrine systems, which influence processes, such as cognition and social behaviour, that are altered in SZ patients [47]. Studies conducted on schizophrenic patients led to intriguing results. Indeed, both treated and untreated patients with SZ showed altered gut microbiota and decreased microbiome heterogeneity compared with healthy controls. Moreover, some unique bacterial taxa and high Lactobacillus gut levels were related to the severity of the clinical picture in patients with SZ [48][49]. A cross-sectional study that analysed the composition of faecal microbiota in both schizophrenic and healthy subjects through 16S rRNA sequencing showed that the first showed abundances of the Proteobacteria Phylum, Succinivibrio, Megasphaera, Collinsella, Clostridium, Klebsiella and Methanobrevibacter. Therefore, the authors proposed a microbiota-based diagnosis and prognosis of SZ [50]. A study conducted on first-episode schizophrenic patients reported altered microbiota composition that was significantly modulated by risperidone, a first-generation antipsychotic (FGA), an effect possibly related to drug-induced metabolic changes [51]. Further evidence suggests that antipsychotics may indeed affect microbiota levels in patients with SZ, specifically in regard to the taxonomic distribution in the case of chronic treatments [52]. The effects of antipsychotic may also be boosted by some antibiotics, such as minocycline, which are able to modify the gut microbiota [53]. However, evidence on this matter is still controversial, as different studies did not detect similar effects of APs in the modulation of gut microbiota [54][55]. Again, the gut microbiota has been proposed as a factor that is responsible for the lack of response observed in some schizophrenic patients [56]. On the other hand, it was

pointed out how probiotics showed no clinical utility in both negative or positive symptoms, albeit only three studies were fully reviewed [57]. Interestingly, in a murine model, inulin, which is a dietary fibre mainly produced by plants [58], was also proposed as a potential treatment in SZ patients due to its anti-inflammatory action and the effects exerted on the gut microbiota [59].

Recently, the relationship between the gut microbiome and brain morphological and functional correlates was investigated in patients with SZ. At the genus level, compared to healthy control subjects, SZ patients displayed a higher abundance of Veillonella, whilst the abundance of Roseburia and Ruminococcus was lower. Moreover, a comparison of MRI images highlighted significant differences in both the volume of gray matter and the regional homogeneity amongst the two groups and higher amplitudes of low-frequency fluctuation in SZ patients. Finally, both changes in gray matter volume and regional homogeneity correlated with the diversity of the gut microbiota [60]. In a similar fashion, significant changes in the volume of the right middle frontal gyrus seem to be related to the specific composition of gut microbiota in SZ [52]. Besides the hypothesis stating that altered gut microbiota might cause the abnormal activation of the immune system, making the gut barrier more susceptible to micro-environmental changes and leading to neuro-inflammation processes involving microglia-mediated neuronal damage, apoptosis, abnormal brain development and altered connectivity between brain regions, even epigenetic modulation might be a mechanism underlying the link between microbiota and SZ [61]. Indeed, gut microbiota might affect gene expression through acetylation and methylation processes in response to environmental cues, possibly constituting a link between environmental risk factors and epigenetic changes [62][63].

Since more specific data on these disorders are lacking, more in-depth studies are warranted to better understand the possible links between gut microbiota and EDs (**Table 1**).

Table 1. Studies on the relationships between gut microbiota and eating disorders.

Authors and Year	Type of Study	Findings
Santonicola et al., 2019 [64]	Review	- Differences in alpha-diversity and composition of microbiota in EDs, possibly contributing to symptomatic manifestations and pathophysiology;
Seitz et al., 2019 [65]	Review	- Decreased alpha-diversity in AN, which showed an increase during weight restoration and a correlation with depressive and anxious symptoms; - Increased beta-diversity in AN, which decreased after weight rehabilitation; - Specific taxa abundance in AN could influence gut permeability, inflammation and symptomatic manifestations

Authors and Year	Type of Study	Findings
Seitz et al., 2019 [66]	Review	- Decreased diversity and taxa abundance in AN; - AN-related changes in microbiome could increase gut permeability, inflammation and autoantibody formation; - Increased microbiome diversity in AN associated with depressive, anxious and EDs symptoms

Legend: AN—anorexia nervosa, ED—eating disorders.

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