The "psychomicrobiotic": Targeting microbiota in major psychiatric disorders: A systematic review

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Review

The "psychomicrobiotic": Targeting microbiota in major psychiatric disorders: A systematic review

Le microbiote intestinal : un rôle potentiel dans les troubles psychiatriques majeurs

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ABSTRACT

The gut microbiota is increasingly considered as a symbiotic partner in the maintenance of good health. Metagenomic approaches could help to discover how the complex gut microbial ecosystem participates in the control of the host's brain development and function, and could be relevant for future therapeutic developments, such as probiotics, prebiotics and nutritional approaches for psychiatric disorders. Previous reviews focused on the effects of microbiota on the central nervous system in in vitro and animal studies. The aim of the present review is to synthetize the current data on the association between microbiota dysbiosis and onset and/or maintenance of major psychiatric disorders, and to explore potential therapeutic opportunities targeting microbiota dysbiosis in psychiatric patients.

RÉSUMÉ

Le microbiote intestinal est considéré de plus en plus comme un partenaire symbiotique contribuant au bon état de santé général de l'organisme. Les approches métagénomiques, en pleine expansion, permettent de mieux en mieux appréhender la complexité de l'écosystème intestinal et de son impact sur le développement et le fonctionnement du système nerveux central de son hôte. Elles pourraient permettre à l'avenir le développement de thérapeutiques spécifiques ciblant le microbiote intestinal, comme les probiotiques, les prébiotiques et les approches nutritionnelles chez les patients souffrant de troubles mentaux. Ces traitements existent déjà dans le traitement de certaines pathologies intestinales, mais l'efficacité, le type de souches, la quantité et la durée administrée restent à déterminer chez l'humain, alors que les résultats animaux sont très prometteurs dans les modèles de troubles anxieux et de stress chronique. Le but de la présente revue est de synthétiser les données actuelles, d'une part, sur l'association entre la dysbiose du microbiote intestinal et le déclenchement ou

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l'entretien de troubles psychiatriques, et d'autre part, d'explorer les thérapeutiques potentielles qui pourraient être proposées aux patients souffrant de troubles psychiatriques associés à une dysbiose intestinale.

1. Introduction

Mood and anxiety disorders, schizophrenia and other mental, neurological and substance-use (MNS) disorders represent 13% of the global burden of disease [1]. While forecasts predict an increase in the prevalence of mental health disorders in the worldwide general population, the response rate to classical psychiatric treatment remains unsatisfactory. Resistance to psychotropic drugs can be due to clinical, pharmacological, pharmacokinetic, and pharmacodynamic factors. Among these factors, recent animal findings suggest that microbiota may have an underestimated influence on its host's behavior and on drug metabolism that may explain ineffectiveness or increased side-effects of psychiatric medications such as weight gain [2].

Microbiota refers to the set of microorganisms that live in a specific environment. The human gastrointestinal tract harbors a microbiota of over 10^{14} bacteria (mostly anaerobic), yeasts, fungi and viruses [3], which means that there are 10 times more prokaryotic cells than eukaryotic cells in the human organism.

Figures are even more impressive from the genes' perspective; it is estimated that the intestinal "microbiome", i.e. the collective gene repertoire of the organisms comprising the gut microbiota, contains well over 150 times more unique genes than the human genome [4]. The role of microbiota has been underestimated until recent years and could be of major importance in regulating multiple vital functions of the body.

The human microbiota composition is host-specific, relatively stable in short time [5]. The microbiome is mainly composed of two bacterial phyla, Bacteroidetes and *Firmicutes*, other such as Proteobacteria, Actinobacteria, Fusobacteria, Archaea and Verrucomicrobia phyla are also present but in relatively small quantities [6]. Microbiota matures in the first three years of life [7] and has a physiological fundamental role in intestinal motility and in the development of the metabolic and immune systems (mucosal and systemic) [8], thus protecting the host against pathogens, participating in the digestion of meals and drugs, and influencing fat absorption and distribution [2,9,10]. Hosts also benefit from several other properties of the intestinal microbiota: vitamin K synthesis, trophic effects on intestinal epithelial cells, energy salvaging from unabsorbed food by short-chain fatty acids (SCFA) production, growth inhibition of pathogens, maintenance of the intestinal barrier integrity and mucosal immune homeostasis and participation in the xenobiotic metabolism system [11].

Several excellent recent reviews summarized fundamental data on microbiota's influence on the central nervous system, based mainly on in vitro and animal studies and, in humans, on inflammatory bowel disorders [12,13]. The objective of the present article was to summarize the current data on microbiota's potential role in psychiatric disorder genesis and/or maintenance, and to explore the potential new therapeutic opportunities targeting microbiota's dysbiosis in psychiatric disorders.

2. Material and methods

2.1. Search strategy

Although the present review is a narrative review, due to the lack of data and the paucity of studies in humans, the present work was based on the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement [14]. PubMed (from 1966 to September 2013), Embase (from 1980 to September 2013), PsychINFO (from 1806 to September 2013), BIOSIS (from 1926 to September 2013), Science Direct (from 2006 to September 2013), and Cochrane CENTRAL (from 1993 to September 2013) were explored, without any year or language restrictions. Duplicates were discarded. Additionally, the reference list of the retrieved articles and relevant review articles were examined for cross-references. A specific search strategy was developed for the interface PubMed (MEDLINE database), based on a combination of MeSH terms: "gut microbiota" or "colon*" or "intestin*" or "pro/prebiotic" or "fecal transplantation" or "brain-gut axis" or "bacteria" with the words: "depression" or "depressive disorder" or "mood disorders" or "bipolar disorders" or "affect" or "seasonal affective disorder" or "affective disorders, psychotic" or "anxiety" or "anti-anxiety agents" or "autistic disorder" or "child development disorders, pervasive" or "psychotic disorders" or "antipsychotic agents" or "schizophrenia". Research by replacing "microbiota" with "metagenome" did not provide additional references. The last search was conducted September 21th, 2014.

2.2. Criteria for selecting articles

Two of the authors, G.F. and W.B., consecutively analysed the articles. Studies were included if they met the following criteria:

- all animal studies addressing the influence of microbiota on central nervous system in both physiological and pathological conditions;
- all clinical studies addressing the influence of microbiota on major psychiatric illnesses, or illnesses with high psychiatric comorbidities;
- all clinical trials assessing microbiota-targeted treatments in major psychiatric disorders (including probiotics, prebiotics, diet, antibiotherapy, activated carbon and faecal transplantation).

A descriptive and explanatory qualitative approach was chosen for the content analysis.

The manuscripts of the studies were then independently reviewed by two of the authors (G.F. and W.B.). Any discrepancies were resolved by consensus with a third reviewer (R.T.).

3. Results

Overall, 1089 abstracts were screened of which 183 articles that studied the association between gut microbiota and central nervous system functioning or psychiatric disorders were included in the present review. The following issues were identified:

- microbiota dysbiosis and putative consequences on central nervous system functioning;
- chronic microbiota dysbiosis-associated illnesses in humans;
- microbiota-oriented treatments and their potential therapeutic applications in psychiatry.

3.1. Microbiota dysbiosis and putative consequences on central nervous system functioning

The term "dysbiosis" refers to situations where microbial composition and functions are shifted from their normal beneficial state to another that is deleterious to the host's health. The microbiota dysbiosis may negatively impact CNS functioning through various intertwined pathways that collectively form the "brain-gut axis". These pathways can be described as follows:

- modification of intestinal permeability that allows entry of endotoxins in the systemic blood flow. The lipopolysaccharide (LPS) is a potent pro-inflammatory endotoxin of the cell walls of

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gram-negative bacteria that can alter neuronal activity in the limbic system (e.g. increased amygdala activity) [15] and also activate microglia, thus potentially contributing to chronic inflammation in the host's CNS [16,17]. Leakage of LPS from the intestine might be a trigger for peripheral inflammatory responses that lead to de novo production of cytokines in the brain. Improving the epithelial barrier may reduce traffic of bacteria and their byproducts and hence be a way to stop the inflammatory response;
- neuropeptides synthesis (for a review see [18]);
- modulation of local and peripheral inflammation. The gut microbiota regulates the development of lymphoid structures and modulates the differentiation of immune cell subsets thus maintaining homeostatic interactions between the host and the gut microbiota (for review see [19]). Certain specific bacteria, including members of the Enterobacteriaceae family, appear to be better equipped for survival under the prevailing conditions in the inflamed gut than are the anaerobic commensals dominant in healthy individuals [20]. Given the postulated anti-inflammatory effects of butyrate, it is possible that depletion in butyrate-producing bacteria in dysbiosis may contribute to inflammation [21]. Major depressive disorder [22–25], bipolar disorder [26–28] and schizophrenia [29–34] are associated with a dysregulation of immune responses as reflected by the observed abnormal profiles of circulating pro- and anti-inflammatory cytokines in affected subjects;
- decrease in absorption of beneficial and essential nutrients (e.g. essential amino acids, vitamins, polyunsaturated fatty acids), increase of deleterious compound synthesis (ammonia, phenols, indoles, sulphide and amines) [35–37], reduction of the antioxidant status and increase in lipid peroxidation, increase of carbohydrate malabsorption;
- activation/deactivation of the autonomic nervous system that is directly connected to the nucleus tractus solitarius. This nucleus in turn issues direct noradrenergic ascending projections to brain areas involved in anxiety regulation (namely amygdala [38], basal forebrain cholinergic system and cortex [39,40]);
- modulation of brain-derived neurotrophic factor [41];
- increase of small intestinal bacterial overgrowth and/or gastric/instestinal pathogens (e.g. *Helicobacter pylori*).

3.2. Microbiota dysbiosis-associated illnesses in humans

Chronic inflammatory intestinal disorders were extensively associated with microbiota dysbiosis and are highly comorbid with psychiatric disorders.

3.2.1. Irritable Bowel Syndrome

Irritable Bowel Syndrome (IBS) has been suggested as the paradigmatic brain-gut axis disorder for several reasons, including: frequency in the general population (10% of the population of Western countries), high rates of comorbidity with psychiatric disorders, especially mood and anxiety disorders [42], and statistical association with history of childhood abuse [43]. Acute bacterial gastroenteritis may be the primary risk factor for IBS, as well as the use of some antibiotics that alter the intestinal microbiota [44]. Interestingly in IBS, female-male sex ratio is about 2.5 (similar as in depressive disorders) and females more often present diarrhea as a major symptom ("IBS-D") whereas males more often present constipation ("IBS-C") [43]. IBS microbiota dysbiosis is associated with reduction in bacterial diversity, reduction of the *Firmicutes* phylum, and increased paracellular permeability of the intestinal barrier [45]. Subjects with IBS-D seem to present less species from the *Lactobacillus* genus and those suffering from IBS-C more species from the *Veillonella* genus [44]. Individuals with IBS present cognitive disorders, particularly in emotional memory recall and verbal IQ (for review see [13]).

3.2.2. Autism

Microbiota dysbiosis was mostly studied in autism spectrum disorder (ASD), a neuro-developmental disorder characterized by impaired social interactions and communication, restricted and repetitive behavior, and frequently accompanied by digestive disorders [46–54]. Several teams have studied the intestinal microbiota of the autistic population and found a different composition of various microbial species in comparison to healthy controls. Compared to healthy children, children with autism have been found to have 10 times more *Clostridium* type germs [55,56], increased Bacteroidetes and *Desulfovibrio*, and decreased *Firmicutes* and *Bifidobacterium* species. Intestinal permeability disorders have also been described in autism [48,49,53,54]. One study by Emanuele and colleagues showed increased LPS in the blood of individuals with ASD, a finding that corresponded to increased peripheral IL-6 levels of IL-6, a neuromodulating cytokine [57]. Some studies found increased intestinal permeability in autistic subjects and in their first-degree relatives, suggesting that these changes may be involved in the pathogenesis of the disease rather than in the consequences of autistic behaviors [58–60]. Compared with typically developing children with gastrointestinal symptoms, a subtle, panenteric infiltration of immune cells such as lymphocytes, monocytes, NK cells, and eosinophils was found into the walls of the gastrointestinal tract in some children with ASD [61–63]. When tested, antibiotic treatment of ASD children did not only lead to gastrointestinal improvements, but also to improvements in cognitive skills [64]. However, the existence of a gastrointestinal pathology specific to ASD subjects remains a controversial topic.

3.2.3. Schizophrenia and bipolar disorders

Severance et al. [65] recently measured serological surrogate markers of bacterial translocation (soluble CD14 (sCD14) and lipopolysaccharide binding protein (LBP)) in bipolar subjects ($n = 38$) and schizophrenia subjects ($n = 141$) compared to controls. sCD14 seropositivity conferred a 3.1-fold increased odds of association with schizophrenia (OR = 3.09, $P < 0.0001$) compared to controls [65]. Case–control differences in sCD14 were not matched by LBP. Quantitative levels of LBP, but not sCD14, correlated with BMI in schizophrenia ($r^2 = 0.21$, $P < 0.0001$) [65]. sCD14 and LBP also exhibited some congruency in schizophrenia with both significantly correlated with CRP ($P < 0.0001$). Antipsychotic treatment generally did not impact sCD14 or LBP levels except for significant correlations, especially sCD14, with gluten antibodies in antipsychotic-naïve schizophrenia ($r^2 = 0.27$, $P < 0.0001$). In bipolar disorder, sCD14 levels were significantly correlated with anti-tissue transglutaminase IgG ($r^2 = 0.37$, $P < 0.001$) [65]. The authors concluded that these bacterial translocation markers produced discordant patterns of activity that may reflect an imbalanced, activated innate immune state. Whereas both markers may upregulate following systemic exposure to Gram-negative bacteria, autoimmunity, non-lipopolysaccharide-based monocyte activation and metabolic dysfunction may also contribute to the observed marker profiles [65].

3.2.4. Anxiety and major depressive disorders

Similar data is not available to date in anxiety and mood disorders, yet animal studies suggest that microbiota may play a major role in lifetime stress, anxiety and mood regulation. It has been demonstrated that the experimental administration of the endotoxin LPS in healthy humans can be associated with increased rates of anxiety and depression, in turn associated with increased salivary cortisol, plasma norepinephrine, and pro-inflammatory

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cytokines [66]. In the same study, LPS was found to modulate emotional memory in a dose-dependent manner. Low gastric acid secretion has been reported in patients with severe depressive disorders and has been associated with reversible small intestinal bacterial overgrowth (SIBO), increased intestinal barrier permeability, malabsorption syndrome, diarrhea, abdominal pain, and constipation [67,68]. Another argument for a role of microbiota in anxiety and mood disorders stems from the fact that certain strains of *Lactobacillus* and *Bifidobacterium* secrete gamma-aminobutyric acid (GABA) [69], *Escherichia, Bacillus*, and *Saccharomyces* produce norepinephrine, *Candida, Streptococcus, Escherichia*, and *Enterococcus* produce serotonin, while *Bacillus* and *Serratia* have the potential to produce dopamine [70]. All these neurotransmittors play a major role in depression and action mechanisms of antidepressive agents.

Interestingly, gut commensal bacteria can efficiently detect the presence of *Toxoplasma gondii* in the intestine, and in turn, initiate signals for immune response [71]. History of *T. gondii* infection has been repeatedly associated with higher onset of schizophrenia and bipolar disorders [72,73]. This could be explained by the parasite's disruption of the microbiota.

One of the major fields of research may be the microbiota's role in the unpredictable weight gain of psychiatric patients due to their medication [74–78]. An altered microbiota has been recently described after olanzapine administration in rats (olanzapine is one of the antipsychotics that induces the most weight gain) [79]. Further studies on weight gain and microbiota changes following such treatments are warranted in psychiatric patients.

3.3. Microbiota-orientated treatments and their potential therapeutic applications in psychiatry

3.3.1. Probiotics

In 1899, a *Bifidobacterium* (*Bacillus bifidus communis*) was first isolated by Henry Tissier (of the Pasteur Institute) from a breast-fed infant.

A century ago, Elie Metchnikoff (a Russian scientist, Nobel laureate) postulated that lactic acid bacteria offered health benefits capable of promoting longevity. He suggested that "intestinal auto-intoxication" and the resultant aging could be suppressed by modifying the gut microbiota and replacing proteolytic microbes (such as *Clostridium*) with more useful microbes. He developed a diet containing milk fermented with the bacterium he called "*Bulgarian bacillus*.".

Lilly and Stillwell first introduced the term "probiotics" in 1965 [80]. Probiotics are nowadays generally defined as live microorganisms, preferentially of human origin, that upon ingestion in specific and sufficient numbers confer non-specific health benefits to the host [81]. Probiotics are capable of stabilizing the mucosal barrier by increasing mucin expression, reducing bacterial over growth, stimulating mucosal immunity (secretory IgA), and synthesizing antioxidant substance [82,83]. The main probiotics used in current commercial preparations are lactic acid bacteria including *Lactobacilli* (*casei, reuteri, fermentum, plantarum, paracasei, salivarius, rhamnosus*) and *Bifidobacteria* (*bifidum, infantis, longum*) [84–86].

The idea of treating psychiatric diseases by administering probiotics is not a recent one: in 1910, Dr. George Porter Philips reported that although *Lactobacillus* tablets and powder were ineffective, a gelatin-whey formula with living lactic acid bacteria improved depressive symptoms in melancholic adults [87]. Current evidence for the efficacy of probiotics in miscellaneous illnesses (mainly intestinal disorders) is inconsistent however, and is rendered more complex by the fact that treatment regimens across different studies are highly heterogeneous, with different species/strains, dosages, lengths of treatment and administration methods employed. Probiotics are also found in food intake: an estimated 35% of all lactic acid bacteria isolated from raw fruits and vegetables can survive gastric conditions [88].

The administration of a single *Bifidobacterium* or *Lactobacillus* strain can increase the quantity of both species within the human gut, suggesting that changes in the enteric microbiota may be even larger [89,90]. Rao et al. showed that these modifications were associated with significant improvement of anxiety symptoms in 39 patients with chronic fatigue syndrome treated with daily ingestion of *Lactobacillus casei* for two months [91]. The oral administration of probiotics has also been shown to be beneficial in the reduction of SIBO associated with anxio-depressive disorders [92]. Two weeks daily, administration of *Lactobacillus helveticus* and *B. longum* was found to alleviate anxiety and depressive symptoms in healthy volunteers [93]. Probiotics may therefore be a treatment of interest in all psychiatric disorders in which increased intestinal permeability has been reported, namely depression, anxiety, autism, schizophrenia, bipolar disorder and alcohol dependence. However, orally consumed *L. casei* milk had no significant effect on mood in 132 healthy adults (but with a baseline positive mood), and was associated with potentially negative effects on recall memory [94].

Several species of probiotics have shown an antiproliferative activity on *Clostridium* species [95–99], which has led some authors to suggest probiotic adjunction in autism therapy with mixed results [100].

A recent report of the Evidence-based Southern California Practice Center on 622 studies indicates that the use of probiotics showed no adverse effects in the short and medium term, but the long-term effects of probiotics consumption remain unclear to date [101].

3.3.2. Diet modification

According to Cryan et al. [102], diet is one of the key factors that substantially influences microbiota composition. Wu et al. [103] recently demonstrated in 98 individuals that certain enterotypes were strongly associated with long-term diets, particularly high animal protein and fat consumption (*Bacteroides*) or carbohydrates (*Prevotella*). In the same study, a controlled-feeding study of 10 subjects showed that change in microbiota composition is detected within 24 hours of initiating a high-fat/low-fiber or low-fat/high-fiber diet, but that enterotype identity remained stable during the 10-day study [103]. Adherence to a typical Western-style diet (high-fat and low-fiber carbohydrates) for one month can elevate plasma endotoxin activity by 71%. By contrast, a switch to a low-saturated fat, fiber-rich diet (so-called "prudent" or more traditional diet) for one month can decrease baseline blood endotoxin activity by 38% in healthy adults [104]. A 6-week very low energy diet affected microbiota, in particular *Bidifidobacteria*, but not the mean weight of sixteen obese adults [105]. *Firmicutes* species at baseline predicted the responsiveness of the microbiota to diet modifications in three independent cohorts of obese European adults [106]. The short-term consumption of diets composed entirely of animal or plant products alters microbial community structure and overwhelms inter-individual differences in microbial gene expression. The animal-based diet increases the abundance of bile-tolerant microorganisms (*Alistipes*, *Bilophila* and *Bacteroides*) and decreases the levels of *Firmicutes* that metabolize dietary plant polysaccharides (*Roseburia*, *Eubacterium rectale* and *Ruminococcus bromii*) [107]. Faith et al. used a low-error 16S ribosomal RNA amplicon sequencing method, in combination with whole-genome sequencing of $>$ 500 cultured isolates, to characterize bacterial strain composition in the faecal microbiota of 37 U.S. adults sampled for up to 5 years [108]. Shared strains were recovered from family members but not from unrelated individuals. The consumption of a monotonous liquid diet for up to

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32 weeks indicated that changes in strain composition were better predicted by changes in weight than by differences in sampling interval. The authors concluded that this combination of stability and responsiveness to physiologic change confirms the potential of the gut microbiota as a diagnostic tool and therapeutic target.

Major dietary antioxidant sources such as cocoa, coffee, green tea, blueberries, and curcumin have all been linked in epidemiological studies to increased growth of *Lactobacilli* and *Bifidobacteria* [109,110]. Coffee consumption has been associated with lowered risk of depression and/or cognitive decline [111]. Curcumin prevented LPS-induced intestinal permeability in an experimental model, while green tea reduced LPS-induced "sickness behavior" (a coordinated set of adaptive behavioral changes that develop in ill individuals during the course of an infection) and blood-brain barrier permeability [112]. Due probably to its high content of flavonoids, the consumption of orange juice along with a high-fat/high-carbohydrate (low-fiber) meal prevented elevations in circulating endotoxin, compared to pure water or sweetened water [113]. Long-term intake of honey, a feature of Paleolithic Age and traditional diets, has been shown in animal research to cancel the effects of LPS and to be associated with the growth of *Lactobacilli* and *Bifidobacterium* [114] as well as with decreased anxiety and cognitive decline versus sugar-free and sucrose diet consuming controls [115].

Magnesium levels were reported to be low in people suffering from depression, and were associated with intestinal permeability and quantitative changes to cecal *Bifidobacteria* and *Lactobacilli* in vitro [116]. Zinc, another nutrient consistently linked to depression when long-term intake is suboptimal, can also influence the diversity of the intestinal microbiota and intestinal permeability [117]. These two nutrients are necessary for the activity of intestinal alkaline phosphatase, a critical enzyme involved in preserving the diversity of gut microbiota and decreasing the systemic LPS burden [117].

3.3.3. Prebiotics

Prebiotics are "non-digestible food ingredients that beneficially affect the host by selectively stimulating the growth and/or activity of one or a limited number of bacterial species already present in the colon" [118]. In other words, prebiotics are mainly indigestible carbohydrates that promote the growth and the activity of beneficial bacteria. Commonly used prebiotics include inulins as well as fructo-, galactic- and xylo- oligosaccharides [118]. They are fermented in the colon by resident microbiota into short-chain fatty acids (SCFAs) that have demonstrated anti-inflammatory properties in IBS [119]. The synbiotic combination of a specific oligofructose-enriched inulin and *L. rhamnosus* GG and *Bifidobacterium lactis* for 12 weeks caused a 16% and 18% increase in the numbers of *Lactobacilli* and *Bifidobacteria*, respectively, and a 31% decrease in the numbers of *Clostridium perfringens* [120]. Prebiotics have not been studied as potential add-on therapies in major psychiatric disorders to date, but may be useful in combination to probiotics.

3.3.4. Postbiotics

An emerging approach to strengthening the microbiota is to first identify the molecules that are depleted in a particular disease, and then supplement the diet with either the depleted molecule or a precursor molecule that can be converted to the bioactive molecule by the microbial community. This approach is especially attractive as these postbiotics are an important class of functional molecules used by the microbiota to modulate human health [121,122]. Amino acid derivatives transformed by the gut microbiota make up one class of compounds that are potential postbiotics. For example, indole, which can be derived from tryptophan, decreases indicators of inflammation, pro-inflammatory transcription factors, and pathogen colonization in intestinal epithelial cells while increasing tight-junction resistance and mucin production [123]. Changes in the abundance of butyrate, acetate, and propionate have also been correlated with health deterioration of elderly patients, further underscoring the importance of bacterial SCFA production in GI tract physiology [124].

3.3.5. Antibiotics

Many antibiotics can have unintended and profound effects on the indigenous microbiota. These effects have been used for therapeutic purposes in mental disorders: minocycline, a second-generation tetracycline, showed some therapeutic effects in schizophrenia, depression and alcohol disorders. These effects may be to be related to a change in gut microbiota among other pathways [125,126]. Usually the indigenous microbiota shows a remarkable capacity to recover once the antibiotic course is over. This recuperation can get in the way of therapeutic effects, for example, Sandler et al. showed that 8 weeks of treatment with vancomycin, an active treatment on *Clostridium* bacteria (used in the treatment of *Clostridium difficile* colitis) improved communication and behaviour scores in autistic children, but that these scores decreased again after treatment discontinuation [64]. However, in most cases, the indigenous microbiota does not completely return to its previous state, with some species-level alterations apparently persisting over long periods of time, which could prove helpful in prolonging therapeutic outcomes beyond duration of the antibiotic treatment [127,128].

3.3.6. Faecal transplantation

Faecal transplantation can be seen as the most extreme intervention on gut microbiota. The aim of faecal transplantation is to replace or replenish the intestinal microbiota of a sick individual by transplanting the microbiota from a healthy donor. Recent meta-analyses have reported a success rate of around 90% when faecal transplantation is used to treat refractory *C. difficile* infection [129,130]. However, faecal transplantation is not widely practiced at present due to the inherent risk of introducing novel pathogenic microbes to the recipient. On-going efforts to elucidate the action mechanisms, the effects on the host's immune response and to refine the microbial inoculum may, however, lead to a wider adoption of the procedure in the future [131].

In a guidance posted on its website on July 18th 2013 and published in the Federal Register, the FDA noted that at a recent workshop discussing regulation of faecal transplant, "some healthcare providers stated that applying Investigational New Drug (IND) requirements will make [faecal transplant] unavailable and suggested that an alternative regulatory approach is needed to ensure the widespread availability of [faecal transplant] for individuals with *C. difficile* infection unresponsive to standard therapies." [132].

3.3.7. Activated carbon

Activated carbon (commonly called activated charcoal) is used to treat poisonings and overdoses following oral ingestion. It binds itself to the toxin to prevent stomach and intestinal absorption. Charcoal biscuits were originally sold in England in the early 19th century, as an antidote to flatulence and stomach trouble. Tablets or capsules of activated carbon are still used today in many countries as an over-the-counter drug for diarrhea, indigestion, and flatulence. Activated charcoal administration may therefore improve the detrimental effects of microbiota dysbiosis by binding itself to potential toxins secreted in the digestive tract [133]. Further studies on activated charcoal potential effectiveness on psychiatric symptomatology are warranted.

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4. Conclusion

Research on the role of the human intestinal microbiota in the genesis and/or maintenance of psychiatric disorders is in its infancy but appears as one of the most promising avenues of research in psychiatry. While rodent models suggest that the microbiota plays a fundamental role in the genesis of the HPA axis, the serotoninergic system and the immuno-inflammatory system, and that the microbiota can affect the CNS through multiple pathways, few studies have been carried out on humans. Today, autism is the psychiatric disorder in which the role of the microbiota has been the most studied. Some therapeutic opportunities targeting potential microbiota dysbiosis have already been explored such as probiotic administration or diet modifications, with inconsistent results. Further studies are warranted to determine which patients may benefit from microbiota-oriented therapies.

Disclosure of interest

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