Title

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Journal

Neuroscience Bulletin, 36(9)

ISSN

1673-7067

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Publication Date

2020-09-01

DOI

10.1007/s12264-020-00535-1

Peer reviewed

Neurosci. Bull. September, 2020, 36(9):1071–1084
https://doi.org/10.1007/s12264-020-00535-1

www.neurosci.cn
www.springer.com/12264

REVIEW

Inflammation in Mental Disorders: Is the Microbiota the Missing Link?

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Received: 23 September 2019 / Accepted: 18 March 2020 / Published online: 27 June 2020

Abstract Research suggests that inflammation is important in the pathophysiology of mental disorders. In addition, a growing body of evidence has led to the concept of the microbiota-gut-brain axis. To understand the potential interactions, we begin by exploring the liaison between the immune system and mental disorders, then we describe the evidence that the microbiota impact the immune response in the developing brain. Next, we review the literature that has documented microbiome alterations in major mental disorders. We end with a summary of therapeutic applications, ranging from psycho-biotics to immunomodulatory drugs that could affect the microbiota-gut-brain axis, and potential treatments to alleviate the adverse effects of antipsychotics. We conclude that there is promising evidence to support the position that the microbiota plays an important role in the immunological pathophysiology of mental disorders with an emphasis on psychotic disorders and mood disorders. However, more research is needed to elucidate the mechanisms.

Keywords Mental disorder · Microbiota · Immunology · Neurodevelopment

Introduction

Mental disorders, among which we mainly focus on schizophrenia (SCZ), autism spectrum disorder, mood disorders, and anxiety, rank among the top causes of years lived with disability worldwide [1]. For SCZ alone, the total cost estimates vary between countries, but are estimated to be ~$102 billion in the USA [2]. And "psychosis" is a common manifestation of several psychiatric disorders that range from major depressive disorder with psychosis to bipolar disorder type I with psychosis and SCZ [3]. Psychosis is defined by the presence of delusions, hallucinations, disorganized thinking, grossly disorganized or abnormal motor behavior, and negative symptoms such as diminished emotional expression, avolition, and social withdrawal [4].

Efforts toward defining clear mechanisms that explain the pathophysiology of mental disorders, biologically-based diagnoses, and novel treatments are needed [5]. In this context, much has been documented regarding the possible role of inflammation in mental disorders [6]. In parallel, many studies on the human microbiota have accumulated to the point that the microbiota-gut-brain axis is thought to play a role in neuropsychiatric illness [7–9]. As reviewed elsewhere [10], there are several pathways through which the microbiota can modulate the microbiota-gut-brain axis. These include endocrine pathways mediated

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s12264-020-00535-1) contains supplementary material, which is available to authorized users.

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via cortisol, neural pathways where the vagus nerve and the enteric nervous system are the main routes, metabolic pathways whereby the microbiota produce neurotransmitter precursors like tryptophan but also active substances like short-chain fatty acids (SCFAs), and finally the immune pathway. However, the immune response/inflammation overlaps most with the above pathways, which makes it an almost unavoidable pathway. In the present article, we comprehensively review the reported influence of both the immune system and the microbiota on mental disorders with an emphasis on psychosis. We focus on the pathogenesis of psychosis from a neurodevelopmental perspective, and finally provide perspectives on potential therapeutic applications (Fig. 1).

Inflammation in Mental Disorders and Potential Role of the Microbiota

In this section, we review the evidence, both clinical and from basic science, supporting the existence of a link between mental disorders and inflammation. To date, this link has been explored more than the potential role of the microbiota. We begin by highlighting the epidemiologic data on associations between psychotic and immunologic disorders as well as evidence from the effects of immunomodulatory drugs. Subsequently, we address the mechanisms driven by microorganisms that could alter the immune response. This is followed by theories of the effects of the immune response on neurodevelopment.

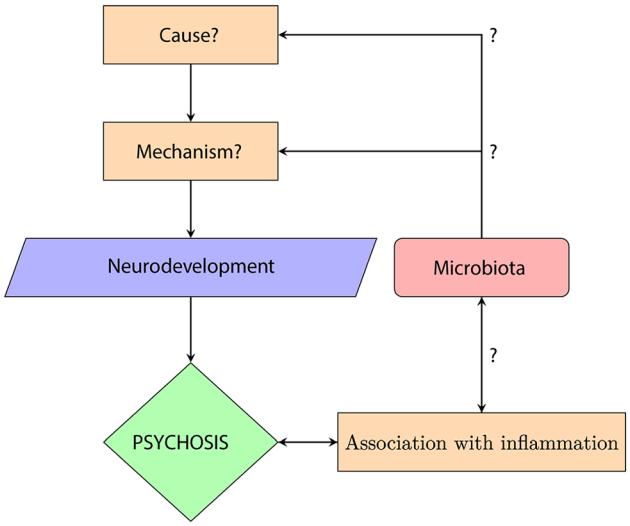

Fig. 1 Summary flowchart. The exact cause and mechanism that explain psychosis remain unknown; however a disruption in neurodevelopment has been documented and is regarded as a pre-stage of psychosis. In parallel, a strong association between psychosis and inflammation has been documented through many sources of evidence. The hypothesis is that the microbiota, which is closely associated with the immune system, may be a piece of the puzzle that explains part of the cause and mechanism of psychosis.

Evidence Linking Mental Disorders to Immunological Disorders

Epidemiological Evidence. Epidemiological evidence links autoimmune and atopic disorders with mental disorders (Table 1). First, a nationwide Swedish study reported an increased risk of affective, personality, and neurotic disorders among individuals hospitalized for systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and ankylosing spondylitis (AS) [11]. They also found an increased risk of psychosis among women with SLE, RA, and AS but not among men [11]. Subsequently, a Danish study based on the records of 7,704 people, found that individuals with SCZ have a 50% lifetime prevalence of autoimmune disorders and that conversely, given a history of autoimmune disorders, the relative risk for SCZ increases by 45% [12]. Associations have been found for celiac disease, RA, autoimmune thyroiditis, type 1 diabetes mellitus (T1DM), SLE, Guillain-Barré syndrome, psoriasis, multiple sclerosis (MS) and autoimmune hepatitis, among others [13]. The case of celiac disease has been studied more extensively. A higher prevalence among patients with SCZ has been documented and immunological markers for celiac disease or gluten intolerance are present in SCZ patients [14]. Anti-gliadin, transglutaminase, and endomysium antibodies, which all participate in gluten sensitivity, are increased in SCZ [14]. Beyond autoimmune disorders, there is also evidence linking atopic disorders in childhood to the development of psychosis in adulthood [15].

Genetic Evidence. The co-occurrence of immunological disorders and mental disorders might potentially be attributed to common etiological factors. These may be genetic or environmental. Genetic evidence supporting a common link between mental disorders and the immune system has been provided by genome-wide association studies that have identified single-nucleotide polymorphisms associated with SCZ in the major histocompatibility complex on chromosome 6 [25]. Innate immunity has also been mechanistically implicated in the appearance of mental disorders [26]. The environmental evidence may be more complicated, but among others, the microbiota can be influenced by variations in both genetic and environmental conditions [27, 28]. This is one of the reasons why we consider that understanding its role in psychotic disorders is pertinent.

Cross-sectional Evidence. Further evidence of inflammation in mental disorders comes from studies during first-episode psychosis. In these patients, an upregulated inflammatory status has been documented by measuring

Table 1 Summary of studies that explore an association between immunological disorders and psychosis.

Reference	Country	Sample characteristics	Associations found
Tiosano *et al.* 2017 [16]	Israel	5,018 SLE patients and 25,090 matched controls	Independent association between SLE and BD
Tiosano *et al.* 2017 [17]	Israel	5,018 SLE patients and 25,090 matched controls	SCZ and SLE
Jackson *et al.* 2014 [18]	USA	100 people with SCZ and 100 matched controls	SCZ and gluten antibodies
Khandaker *et al.* 2014 [15]	UK	6,785 adolescents with psychotic experiences	Atopic disorders prior to psychosis
Benros *et al.* 2014 [13]	Denmark	3.83 million people; 39,364 with SCZ-like psychosis and 142,328 with autoimmune disease	Autoimmune disorders and psychosis
Kumar *et al.* 2013 [19]	India	50 patients with pemphigus, 30 with psoriasis, and 30 matched controls	Psychosis with pemphigus and psoriasis
Kota *et al.* 2012 [20]	India	260 patients with T1DM	Psychosis and T1DM
Sundquist *et al.* 2008 [11]	Sweden	Entire Swedish population	Psychosis and SLE or RA among women
Sturdy *et al.* 2002 [21]	UK	533 cases and 533 controls	Psychosis as a risk factor for death certified as caused by asthma
Gilvarry *et al.* 1996 [22]	UK	101 psychotic and 116 control patients	Family history of psychosis and thyrotoxicosis and T1DM
Nasr *et al.* 1981 [23]	USA	82 psychiatric patients	Atopic disorders and affective disorders
Osterberg, 1978 [24]	Sweden	58 psychiatric cases	SCZ and either RA or AS

SLE, systemic lupus erythematosus; BD, bipolar disorder; SCZ, schizophrenia; T1DM, type 1 diabetes mellitus; RA, rheumatoid arthritis; AS, ankylosing spondylitis.

cytokines such as interleukins 1β and 6, and tumor necrosis factor alpha. Also, adiponectin may play a unique pro-inflammatory role in this patient population [29–32]. Variations seem to exist according to the stage of illness. Specific inflammatory cytokines differ between first episodes, psychotic states, and remission states [33]. In the case of bipolar disorder, possible mechanisms have been reviewed elegantly elsewhere [34].

Evidence from Immunomodulatory Drugs. Another source of evidence is the efficacy of immunomodulatory drugs such as minocycline, non-steroidal anti-inflammatory drugs (NSAIDs), dehydroepiandrosterone, dehydroepiandrosterone sulfate, pregnenolone, polyunsaturated fatty acids, N-acetylcysteine, or L-theanine in the treatment of psychosis, which also suggests an underlying inflammatory process [35]. In addition, there is evidence of an anti-inflammatory effect of antipsychotics in inhibiting microglial activation [36].

Potential Role of the Microbiota

Evidence Linking Immunological Disorders and the Microbiota. In this section, we review evidence linking both atopic and autoimmune disorders to changes in either the normal microbiota or with exposure to infectious agents. According to Okada *et al.* (2010) the "hygiene hypothesis" can be extended from atopic to autoimmune diseases. First, there is epidemiological evidence such as the rise in incidence in places where the sanitation is better, and through migration and geographical distribution studies. Also, a causal relationship has been demonstrated mostly in animal models [37]. Apart from the explanation of T helper 1 (Th1) and Th2 deviation, Okada *et al.* (2010) proposed other explanations such as antigenic competition and bystander suppression by CD4+/CD5+ forkhead box P3 regulatory T cells and mechanisms independent of antigenic stimulation such as the stimulation of Toll-like receptors [37]. Alterations in the microbiota have been documented in autoimmune disorders such as T1DM [38, 39], MS [40], inflammatory bowel disease [41], primary biliary cirrhosis [42], and connective tissue diseases [43, 44] (Table 2).

Signals Driven by Microorganisms. One of the reasons why we consider that the microbiota may play a significant role in mental disorders through modulation of the immune system is because microbial signals drive the balance

Table 2 The hygiene hypothesis: articles on associations between autoimmune disorders and changes in the composition of microbiota.

Reference	Title	Sample characteristics	Associations found
De Groot *et al.* 2017 [38]	Distinct fecal and oral microbiota composition in human type 1 diabetes, an observational study	53 patients with T1DM and 50 matched controls	Decreased *Christensenella* and *Subdoligranulum* are correlated with glycemic control, inflammatory parameters, and SCFAs
Knip *et al.* 2017 [39]	Modulation of type 1 diabetes risk by the intestinal microbiome	Review	Microbiome protects humans against T1DM
Wekerle, 2017 [40]	Nature, nurture, and microbes: The development of multiple sclerosis	Review	Microbiota may contribute to MS pathogenesis
Kim *et al.* 2017 [41]	The interplay between host immune cells and gut microbiota in chronic inflammatory diseases	Review	Role of the microbiota in IBD, MS, allergic asthma, and RA
Quigley, 2016 [42]	Primary biliary cirrhosis and the microbiome	Review	Role of a bacterium in the initiation of the autoimmune process that leads to the development of primary biliary cirrhosis
Talotta *et al.* 2017 [43]	The microbiome in connective tissue diseases and vasculitides: An updated narrative review	Review	The dysbiotic microbiome plays a role in the pathogenesis of SLE, systemic sclerosis, Sjögren's syndrome, and Behçet's disease
Yacoub *et al.* 2018 [44]	Lupus: the microbiome angle	Review	Mechanisms by which the microbiota affects SLE
Lowry *et al.* 2016 [45]	The microbiota, immunoregulation, and mental health: Implications for public health	Review	Environmental microbes modify risk for inflammatory disease, with a focus on neurodevelopmental and psychiatric conditions

SCFAs, short-chain fatty acids; T1DM, type 1 diabetes mellitus; MS, multiple sclerosis; IBD, inflammatory bowel disease; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

between T helper and T regulatory cells [46, 47]. The signals that drive this balance can be metabolites such as tryptophan or SCFAs, microbial molecules that enhance immune regulatory circuits through stimulation of DC-SIGN (dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin) and the Lewis lipopolysaccharide that also binds DC-SIGN, or helminthic molecules such as fucose. These can originate (1) from commensal microbiota, mainly *Firmicutes*, (2) from old infective pathogens such as hepatitis A virus, *Toxoplasma gondii*, *Salmonella spp.*, helminths, nematodes, *Mycobacterium tuberculosis* or *Helicobacter pylori*, and (3) from organisms from the natural environment such as non-tuberculous mycobacteria [45].

Leaky Gut. An altered, more permeable gut barrier has been reported in several disorders such as irritable bowel syndrome [48]. A possible explanation for this increased permeability is a dysbiosis favoring a pro-inflammatory state in the bowel. This allows the passage of inflammatory molecules such as lipooligosaccharide and amino-acids into the bloodstream, causing dysregulation of the immune response and antigen recognition [49]. Thus, we consider that alterations in the microbiota might be both a cause of leaky gut and the leaky gut in turn may be a mechanism through which dysbiosis exerts its effect on the immune and nervous systems. Gut permeability is thus interesting as a parameter to measure, such as by the presence of *Saccharomyces cerevisiae* or *Candida albicans* antibodies. Also, increased levels of these antibodies have been documented in SCZ [50–52].

Inflammation during Prenatal Life and Neurodevelopment. Finally, another perspective from which to view the impact of the immune system on the brain is neurodevelopmental. There is evidence that pro-inflammatory states during prenatal life, especially in the second trimester, are associated with the development of SCZ [35]. These states can be due to maternal exposure to infection or stressful situations such as the loss of a partner, war, obstetric complications, or starvation [35]. In their review, Suvisaari *et al.* (2013) considered three theories: First, that cytokines play a role in brain development in processes like neurogenesis, gliogenesis, proliferation, axon pathfinding, and microglial development. The second theory hypothesizes that microglia are hyperactive in SCZ. The third theory is based on the finding that auto-antibodies, such as anti-brain and antinuclear antibodies, are elevated in SCZ, and proposes that brain-reactive auto-antibodies participate in the pathophysiology of SCZ [35].

Direct Evidence of a Role of the Microbiota in Immunomodulation and Neuroimmunity

We have discussed evidence for a link between the immune system and mental disorders and in parallel between the microbiota and the immune system. The evidence that links these three elements comes mostly from observational studies which we treat in "Microbiota and Abnormal Neurodevelopment" section. Jang *et al.* in 2018 reported that exposure of mice to ampicillin causes anxiety and colitis and changes in the microbiota composition [53]. Then they showed that these changes are accompanied by increased blood corticosterone, interleukin-6, and lipopolysaccharide levels. Also, inflammatory cells such as monocytes and dendritic cells were recruited to the hippocampus. Finally, they demonstrated reversal of the changes and the symptoms following administration of *Lactobacillus reuteri* [53]. In a mouse model, it has been shown that altering the microbiome by means of antibiotics diminishes plaque deposition in the brain [54]. Another experiment, by Wilck *et al.*, also demonstrated a link between the microbiota, T-h17 lymphocytes, and neurological health by treating mice with salt, showing compositional changes in the microbiota and reduced aggravation of induced encephalomyelitis, thus demonstrating the existence of what they call a "gut-immune" axis [55]. The presence of this axis is further supported by experiments in animal models of other brain conditions such as stroke [56]. There are even animal models of depression that are constructed by inducing inflammation [57]. It has also been reported that the signaling of the inflammasome associated with anxiety and depression affects the gut microbiota, suggesting that the communication is bidirectional [58].

Microbiota and Abnormal Neurodevelopment

Microbiota and Early Brain Development

The prenatal and postnatal periods are critical neurodevelopmental windows in mammals, and they overlap with the original microbial colonization [59]. Several disruptions of normal development have been described that contribute to the pathogenesis of psychosis and could be mediated by changes in the microbiota (Fig. 2).

Prenatal Period. Though several studies have supported the notion that the mammalian fetus is not germ-free, as once believed [60], the existence of a placental microbiome is still a matter of debate as the positive findings are thought to issue from contamination [61]. However, there is abundant evidence supporting the influence of the microbiota on neurodevelopment in humans and mice [62].

The most direct evidence comes from prenatal infection and antibiotics studies, which include research on both humans and rodents. Reported results from these assays suggest that infections with *Toxoplasma gondii*, human herpesvirus 2, and *Chlamydophila* have robust links to psychosis in humans [63, 64]. Drawing conclusions about the effects of antibiotics is, in contrast, more complicated and controversial due to the frequent coexistence of infection and the numerous types of antibiotic. Few studies have addressed this in the particular case of psychosis. However, a randomized controlled trial found that macrolide use in pregnant women is associated with an increased risk of childhood cerebral palsy and epilepsy [65], whereas another cohort study did not confirm this result [66].

In rodent studies, maternal exposure to antibiotics increases behavioral abnormalities such as anxiety-like and dissocial behavior in the offspring through perturbations in the microbiota [67, 68].

As well as the above, other factors that have been associated with dysbiotic microbiota and abnormal behavior in the offspring include a high-fat diet [69], maternal immune activation [70], prenatal stress [71, 72], peptidoglycan [73], and propionic acid [74].

Time and Mode of Delivery. The microbiota composition has been shown to differ between preterm and term infants [75]. Preterm infants have an increased risk of psychiatric or behavioral problems later in life [76, 77]. Another aspect that has been studied is the mode of delivery and the results are conflicting. One study reported that cesarean delivery is associated with an increase in psychosis among offspring [78] while another found no significant difference [79]. However, it is known that cesarean delivery is associated with colonization by microbes from the skin instead of the vagina [80]. The mechanisms by which the microbiota is involved in the development of psychosis later in life are not yet fully understood, however its potential involvement makes it worthy of further study.

Postnatal Period. Under normal conditions, infants are exposed to environmental and maternal microbes immediately after birth. As previously stated, the mechanisms by which the microbiota interacts with neurodevelopment remain elusive, the results of potential association studies being very varied. For example, several studies on germ-free animals have shown various abnormalities in behavior, including reduced social behavior and memory deficits [81, 82]; conversely, several studies have indicated that germ-free mice have less anxiety-like behavior and more motor activity than specific pathogen-free mice [9, 83]. In addition, probiotic and antibiotic interventions have been reported to alter neural responses in germ-free mice by mediating the hypothalamic-pituitary-adrenal axis or brain-derived neurotrophic factor [84–86]. Overall, a significant

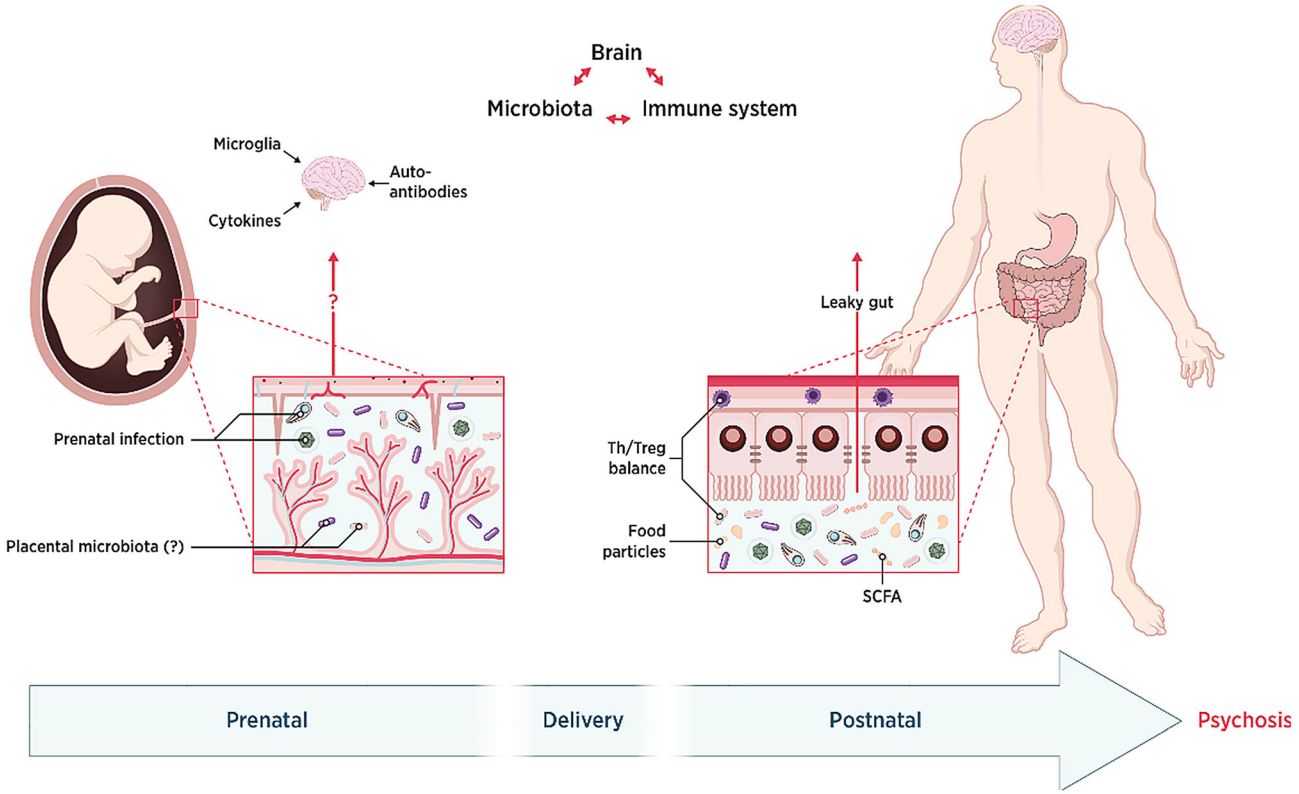

Fig. 2 Role of the microbiota-gut-brain axis during neurodevelopment. We focus on three main critical periods. First, in the postnatal period, although there is consensus about the absence of placental microbiota, microbial disturbance caused by prenatal infection or the administration of antibiotics could impact brain development through diverse pathways. Second, microbial colonization of the newborn takes place differently depending on the mode and time of delivery and this impacts general health. Finally, during the postnatal period or even adulthood, the microbiota-gut-brain axis still functions through neural, endocrine, and immunological pathways, a particular one being the leaky gut. In the end, abnormal development of the brain might lead to psychosis.

body of documentation supports the idea that the gut microbiota affects neurodevelopment during the postnatal period.

Specific Evidence of an Association between the Microbiota and Mental Disorders

Ultra-high Risk for Psychosis. Our recent study found that the levels of *Clostridiales*, *Lactobacillales*, and *Bacteroidales* are higher in fecal samples from ultra-high risk individuals than genetic high-risk subjects and healthy controls [87]. Combining this with magnetic resonance spectroscopy brain scans we hypothesized that compositional changes of gut microbiota might activate microglia in the brain through the elevation of SCFAs.

Schizophrenia. Unlike the ultra-high risk situation, which only has one related study, there have been many studies investigating the gut microbial composition in SCZ cohorts. Among these are 3 longitudinal studies, with treatments ranging from 6 weeks to 12 months. Two studies found significant changes in the gut microbiota after treatment [88, 89]. However, the other study showed non-significant results, possibly because of the non-first-episode subjects and the shortest intervention period – only 6 weeks [90]. Also, case-control studies have compared the gut microbiome diversity between SCZ patients and healthy controls [91–94]. Two studies found that SCZ is associated with reduced richness of the gut microbial composition [92, 93], but the other two failed to show consistent results [91, 94]. What is more, the differences in taxonomic composition between SCZ patients and healthy controls are even more complicated and heterogeneous. For example, the abundance of *Clostridium* was found to be increased in SCZ patients from two studies [91, 93], but the situation was just the opposite in another study [94]. All the above cases reflect the dilemma of microbiome studies of mental illness, which display high heterogeneity and difficulties with replicability.

Separately, two oropharyngeal microbiome studies have been conducted on the same population. One found that the level of *Lactobacillus* phage phiadh was significantly higher in SCZ patients than controls [95], and the other showed that *Ascomycota, Lactobacilli*, and *Bifidobacterium*, which have been associated with chronic

inflammation, are more abundant in SCZ patients than controls [96].

In addition, several serological studies indirectly support the existence of differences in the microbiome of SCZ patients [97–99]. Torrey *et al.* (2007) conducted a meta-analysis and showed that antibodies to *T. gondii* are increased in individuals with SCZ [97]. Severance *et al.* (2012) detected an elevation of IgG antibodies to *S. cerevisiae* in SCZ compared to controls in 2012, and in 2016 found that *C. albicans* seropositivity increases the odds for SCZ in males [97, 98]. Houenou *et al.* found that higher *Cytomegalovirus* serointensity is related to right hippocampal volume in both SCZ and bipolar disorder patients [99]. A recent systematic review by Nguyen *et al.* (2018) found five microbiome studies and five translocation studies on SCZ, bipolar disorder, or other severe mental illness. Although the authors pointed out limitations in the literature reviewed, they found an association between reduced microbial diversity and other global community differences in patients with SCZ and bipolar disorder [100].

Beyond human studies, Zhu *et al.* and Zheng *et al.* transplanted fecal microbiota from SCZ patients into specific pathogen-free mice and caused SCZ-like behaviors [92, 101]. After that, they suggested that the abnormal behaviors might be induced by subsequently dysregulated kynurenine metabolism or a disrupted glutamate-glutamine-GABA cycle from the morbid gut microbiota.

Autism Spectrum Disorders. At the genus level, *Clostridium* [102–104], *Lactobacillus* [105–107], *Sutterella* [108–110], and *Desulfovibrio* [106, 111] have often been identified in increased proportions in fecal samples from autistic children. And *Prevotella*, *Coprococcus*, and unclassified *Veillonellaceae* have been reported to occur in low abundance in fecal samples from autistic individuals [112]. However, some research data did not show differences in gut microbiota between autistic children and their neurotypical siblings [113]. Like in human samples, the mouse model of autism also showed consensus results that the phyla *Bacteroidetes* and *Firmicutes* and the order *Desulfovibrionales* are associated with autistic behaviors [74, 114, 115]. And interestingly, treatment with *L. reuteri* [116] and *B. fragilis* [114] can reverse some of the core symptoms of autism, such as social deficits and stereotyped behaviors. Also, Chen *et al.* found that deficiency of KDM5 demethylase causes autistic behaviors in flies through gut dysbiosis, and the administration of *Lactobacillus plantarum* restores the behavioral impairments [117]. Compared to adult psychosis, autism usually develops in early life and seems to have fewer psychological factors. Hence, the gut-brain axis is expected to play a role in the etiology and cure of this disabling disease.

Mood Disorders. The topic of gut microbiota and mood disorders has been widely studied. The phylum *Actinobacteria*, the order *Bacteroidales*, and the genus *Oscillibacter* have been consistently reported to be over-represented in association with depression, in both patients and rodent models [118–121]. Perhaps due to the difficulty of establishing animal models of bipolar disorder (especially mania), almost all evidence is from human studies. And increased *Bacteroidetes* and *Clostridiales* and decreased *Faecalibacterium* have been repeatedly reported in individuals with bipolar disorder [122–126]. Furthermore, Hu *et al.* considered that the decreased *Faecalibacterium* and other butyrate-producing bacteria might contribute to bipolar depression, and treatment with Quetiapine could change the microbial composition [123].

Anxiety and Stress-related Disorders. That stressor exposure alters the gut microbiota in rodents and humans has been well studied. The results have shown a decrease of *Lactobacillus* and an increase of *Lachnospiraceae* after stress [81, 127–129]. The fact that both parasite-infected mice and those on an altered diet show anxiety-like behavior strengthens the hypothesis that the microbiota plays a role in anxiety and stress-related disorders [84, 130]. Also, an exploratory study demonstrated that decreased total abundance of *Actinobacteria, Lentisphaerae,* and *Verrucomicrobia* is associated with more severe symptoms of post-traumatic stress disorder [131]. Whether germ-free rodents show increased or reduced anxiety-like behavior has not yet been consistently established [9, 132]. The influence of the gut microbiota on anxiety and stress-related disorders warrants further investigation.

Overall, most of the specific evidence either points to the regulation of the immune system or neurotransmitters. And because of all the limitations of animal studies and the conclusions drawn from them, translational studies are critically needed in this field. A summary of studies that explored microbial influence during neurodevelopmental windows and subsequent mental disorders is detailed in the supplementary material (Table S1).

Prospective Therapeutic Applications in Mental Disorders

Probiotic Studies

A probiotic is a live organism that, when ingested in adequate amounts, exerts a health benefit. Their use in mental illness has been reviewed more extensively elsewhere [133]. Several members of the microbiota are known to produce neurotransmitters such as dopamine, gamma-aminobutyric acid (GABA), norepinephrine, serotonin (5-

HT), acetylcholine, and endocannabinoids [134]. The fact that the intestinal microbiota produces neuroactive compounds is one of the reasons why it is pertinent to study and test its therapeutic potential. Dinan *et al.* (2013) define a psychobiotic as such a substance that produces a health benefit in patients suffering from psychiatric illness [134]. It has been reported that 5-HT plasma levels are significantly higher in normal mice than in germ-free mice [135]. This, together with the finding that ingestion of *Bifidobacterium infantis* in rats increases the levels of tryptophan [136], supports the hypothesis that the microbiota plays a role in the modulation of neurotransmitter levels and possibly also mood. Furthermore, the gut microbiota has been shown to affect the levels of brain-derived neurotrophic factor in the brain [84]. It has even been postulated that the microbial colonization of the newborn and infant participates in modulating the development of the hypothalamic-pituitary-adrenal axis [86]. It has also been demonstrated that the regulation of mood by the gut microbiota is mediated by the vagus nerve as it disappears when the vagus is sectioned [137]. The gut microbiota has also been implicated in anxiety regulation in animal models [83, 138].

The use of psychobiotics has been studied in humans in terms of stress [128, 133, 139–142], anxiety [133, 142–145], and mood [133, 142–145]. However, there is little evidence to support the clinical use of psychobiotics and their efficacy. In a systematic review, Romijin *et al.* [146] studied the evidence behind the use of psychobiotics in humans. Their search led to a preselection of ten studies of various mental disorders, none of which showed a statistically significant difference after the administration of probiotics. They selected only one study concerning SCZ in which Dickerson *et al.* (2014) found that repeated-measures analysis of variance showed no significant differences in the total score on the Positive and Negative Symptom Scale (PANSS) between probiotic and placebo supplementation [147]. Romijin *et al.* (2015) concluded that there is little supporting evidence for the use of psychobiotics in humans, and recommended that further research be conducted in affected populations while taking into consideration the duration of the intervention period and the probiotic strain [146]. Nonetheless, a more recent study by Dickerson *et al.* has shown fewer re-hospitalizations after mania with psychobiotic administration [148].

Anti-inflammatory or Immunomodulatory Drugs and Dietary Modifications as Add-on Therapy in Mental Disorders

NSAIDs, aspirin, omega-3 fatty acids, and minocycline have been tested on the symptoms of SCZ, and there is evidence that they are modestly effective [149, 150]. The second-generation tetracycline minocycline has been tested in humans for the treatment of SCZ. In a systematic review and meta-analysis of six randomized controlled trials by Solmi *et al.* (2017), it was found that minocycline has significant beneficial effects, particularly on improving the negative symptoms. In the PANSS the standardized median difference (SMD) was – 0.59 with a confidence interval of [–0.88, –0.00] and a P = 0.04. A difference in negative symptoms was also documented (SMD = –0.76, CI = [–1.21, –0.31], P = 0.001). It also has positive effects on cognitive symptoms such as attention and vigilance as well as executive functioning. More trials are necessary to study the effect on positive symptoms [151]. Whether it acts through modification of the microbiota, immunomodulation, or another mechanism remains to be determined [152].

Finally, according to a revision by Kalaydjian *et al.* (2006) there is evidence from ecological studies, prevalence studies, clinical trials that include dietary recommendations, and immunological and genetic findings, that supports the view that SCZ and celiac disease may be heterogeneous presentations of a similar cause and that individuals with SCZ could benefit from dietary modifications [153].

Adjuvant Therapy to Counteract Antipsychotic Side-effects

Antipsychotic medication is known to cause long-term metabolic side-effects such as metabolic syndrome, dyslipidemia, weight gain, insulin resistance, T2MD, and cardiovascular disease [154–160]. In an attempt to assess the mechanisms underlying these adverse effects, Davey *et al.* (2012) studied the consequences of olanzapine administration in rats. Olanzapine-treated rats had an increase in *Firmicutes* and a decrease in *Bacteroidetes* [161] which coincided with the microbiome changes already documented for obesity in humans [162]. To investigate whether the microbiota is directly involved in the metabolic effects of olanzapine, in a second study, Davey *et al.* [163] administered broad-spectrum antibiotics to rats and found that they attenuated the side-effects of olanzapine. Moreover, they found that when antibiotics were administered along with olanzapine the increase in *Firmicutes* and decrease in *Bacteroidetes* no longer occurred. This was later confirmed with risperidone when Bahr *et al.* [164] demonstrated that one of the mechanisms by which risperidone causes weight gain is a decrease in energy expenditure. Interestingly, when they transplanted into naïve mice feces from mice that had suffered weight gain after risperidone administration, these naïve mice also experienced weight gain, demonstrating that changes in the microbiota alone are sufficient to cause weight gain. The

same group also documented changes in the microbiota coherent with those described in obesity among children taking risperidone chronically [165].

It has recently been reported that ~24% of prescription drugs inhibit bacterial growth *in vitro*, and, despite their chemical variability, antipsychotics are one of the groups most notorious for their inhibition of bacterial growth, and it has been proposed that this may be involved in the mechanism of action of these drugs [166].

Although causality and mechanism cannot yet be established, the manipulation of the microbiota by the use of prebiotics, probiotics, dietary modifications, or even antibiotics is a promising tool when it comes to palliating the adverse effects of antipsychotics on energy metabolism. Furthermore, changes in the microbiota may be involved in the mechanism of action of antipsychotics.

Conclusions

Psychotic disorders are highly disabling, hence efforts to understand their pathophysiology are of the utmost importance. It has been extensively documented that inflammation plays a role in these phenomena, as shown by the association between mental disorders and immunological alterations in epidemiological studies.

We have reviewed studies that show an association between prenatal infection and antibiotic use during the windows of development (prenatal, during delivery, and during the postnatal period) that affect the maternal microbiota and might impact brain development. The major drawback of the included studies is that most of them are descriptive of associations and fail to provide insight into the causality and mechanisms of the observed phenomena. Other limitations included small sample sizes and the diversity of differences in the microbiotas of cases and controls. Therefore, there is a clear need for more reports that elucidate the mechanisms by which disturbances in the microbiota cause changes in the gut and the immune system and how these translate into brain pathology. We can still conclude that there is enough evidence to suggest a role for the microbiota and the immune system in the pathophysiology of mental disorders. And further exploration of how suspect microbiota affect the existing psycho-immunology pathway might be a short-cut in this field. In short, investigation of the microbiota-immune-brain axis is a promising field for future study as it may both shed light on one of the mechanisms underlying mental disorders as well as be a source of therapeutic interventions and diagnostic tools such as potential biomarkers. We hope that soon the collective effort in microbiome research will translate into bench interventions and public health recommendations.

Acknowledgments This review was supported by the National Natural Science Foundation of China (81871056). We would like to thank Okko Alitalo, MSc, from the Laboratory of Neurotherapeutics of the Faculty of Pharmacy at the University of Helsinki for designing figure 2. We would also like to thank Dr. Henriette Raventós and her team at the Cellular and Molecular Biology Research Centre of the University of Costa Rica for their corrections and comments on this paper.

Conflict of interest The authors claim that there are no conflicts of interest.

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