Dysregulation of the gut–brain axis in schizophrenia and bipolar disorder: probiotic supplementation as a supportive treatment in psychiatric disorders

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Purpose of review
Schizophrenia (SCZ) and bipolar disorder are severe mental disorders, both placing a significant burden on individuals' wellbeing and global health generally. The complex interaction of multiple mechanisms, underlying these disorders, still needs further elucidation. Increased activation of components of the immune system may be involved, including alterations in intestinal permeability and gut microbiome. Probiotics, defined as living microorganisms conferring health benefits to the host when administered in adequate amounts, seem to have supportive therapeutic effect in psychiatric disorders. The authors in this review provide an overview of this emerging research field and summarize both the publicated microbiome studies in SCZ and bipolar disorder and the current clinical research using probiotic supplementation in patients diagnosed with these disorders.

Recent findings
The current data indicate that there are differences in the microbiome in SCZ and bipolar disorder patients as compared with healthy controls. Part of these differences may be induced by medication use, others by smoking and other lifestyle factors. Correlations between microbiome quantification and symptom severity have been observed in cross-sectional studies, but unfortunately, no replicated findings so far. Probiotic supplementation was shown not only to alleviate gastrointestinal complaints but also reduce symptom severity, rehospitalization rates and cognitive improvement. Replication of improvement of cognition is needed.

Summary
Differences in microbiome have been shown in both SCZ and bipolar disorder in comparison to healthy controls. Evidence that probiotics can improve psychiatric functioning is still very limited.

Keywords
bipolar disorder, gut microbiome, gut–brain axis, inflammation, intestinal permeability, probiotic supplementation, probiotics, schizophrenia

INTRODUCTION

Current worldwide estimates of schizophrenia (SCZ) and bipolar disorder patients are 23 and 60 million people, respectively [1]. Although the introduction of antipsychotics in the 1950s has substantially improved clinical symptoms of SCZ [2], the disease is still causing considerable morbidity and mortality [3]. In bipolar disorder, lithium is, for many years, the first-choice maintenance-treatment with anticonvulsants and antipsychotics as major alternatives. However, up to 50% of bipolar disorder patients do not respond adequately and still suffer from manic and/or depressive episodes, often severely affecting functioning [4].

Both psychiatric disorders are characterized by imbalances in the gut microbiome, which comprises

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KEY POINTS

- Increased intestinal permeability links the gut microbiome dysbiosis and neuro inflammation in SCZ and bipolar disorder.
- Current clinical research on the intestinal microbiome shows alterations in both SCZ and bipolar disorder.
- Current clinical research on using probiotics supplementation is minimal and inconsistent, with some studies demonstrating biological and clinical efficacy in SCZ and bipolar disorder.

the resident bacteria in the human intestine [5–7], peripheral inflammation associated with increased intentinal permeability, caused by impaired tight junction functioning [8], and consequently alterations in the systemic immune system [9–11].

Increased intestinal permeability, reported in both SCZ and bipolar disorder, leads to translocation of bacterial and food-derived antigens from the intestinal lumen to the systemic circulation. Leaking Gram-negative bacteria can stimulate the production of proinflammatory cytokines, such as IL-6 and IL-1b, through binding of the lipopolysaccharide (LPS) component of their cell walls to Toll-like receptors (TLRs; i.e. TLR-4), expressed on monocytes, macrophages and microglia. The released proinflammatory cytokines signal to the brain peripherally via the vagus nerve or directly via the circumventricular organs (regions of the blood–brain barrier with relative permeability) [12,13]. Microglia, resident macrophage-like cells in the central nervous system (CNS), is one of the main components in developing the whole CNS neural circuitry [14]. Therefore, overactivation of the proinflammatory cytokines can affect the patterning and wiring within the CNS [15–17] (Fig. 1).

Probiotics are defined as living microorganisms conferring health benefits to the host when administered in adequate amounts [18]. The main bacterial genera used as probiotics in both animal and human studies are the *Lactobacillus* and *Bifidobacterium* genera [18–21]. Probiotics are now available as tablets, capsules, sachets, wafers, in fermented milks or drinks, in yogurts and cheese and even in chocolates. Currently, they can be obtained from pharmacies, drugstores, grocery stores, health food stores or from webshops [22]. Recently, Dinan *et al.* [23] proposed the concept of 'Psychobiotics' to emphasize the potential of probiotics in the treatment of mental disorders.

Hence, a better understanding of gut microbiome dysbiosis and its involvement in the development of SCZ and bipolar disorder could enhance the treatment outcomes. This review aims to provide an overview on this emerging research field and summarize the existent microbiome studies in SCZ and bipolar disorder. This review also summarizes current clinical research using probiotic supplementation to improve symptoms and cognition in patients with severe mental disorders.

OVERVIEW OF CURRENT CLINICAL RESEARCH ON MICROBIOME DYSBIOSIS IN SCHIZOPHRENIA AND BIPOLAR DISORDER

Compiled data from the MetaHit and the Human Microbiome Project identified 2172 species isolated from human beings, classified into 12 different phyla, of which 93.5% belonged to *Proteobacteria*, *Firmicutes*, *Actinobacteria* and *Bacteroidetes* [24]. The *Bacteroidetes* and *Firmicutes* are conserved almost in all individuals, although the relative proportions of these phyla may vary [25]. However, when considered at the level of bacterial species, the variation in the composition of interindividual microbial communities is considerably greater than that observed at the phylum level [26].

Gastrointestinal tract

There is a total of seven studies on the gut microbiome composition in both SCZ and bipolar disorder published within the past 2 years. Out of the total seven published studies, there were two performed in SCZ patients and five in patients diagnosed with bipolar disorder (Table 1).

The study of Nguyen *et al.* [27▪▪] was the first to provide evidence for an altered intestinal microbiome in 25 chronic SCZ patients in the United States with reference to 25 nonpsychiatric comparison controls. After controlling demographic and clinical factors that may influence microbial composition, significant differences in the overall composition and levels of specific bacterial taxa in the intestinal microbiome between the two groups were found. Differences in abundance for multiple taxas have been observed between groups, including decreased relative abundance of phylum *Proteobacteria* and genera *Haemophilus, Sutterella* and *Clostridium* and increased relative abundance of genus *Anaerococcus* in SCZ patients compared with nonpsychiatric comparison controls. In addition, they found that the composition of the intestinal microbiome was associated with psychopathology. Increased *Ruminococcaceae* was correlated with decreased negative symptoms while increased *Bacteroides* with worsened depressive symptoms. However, the study had several limitations as a small

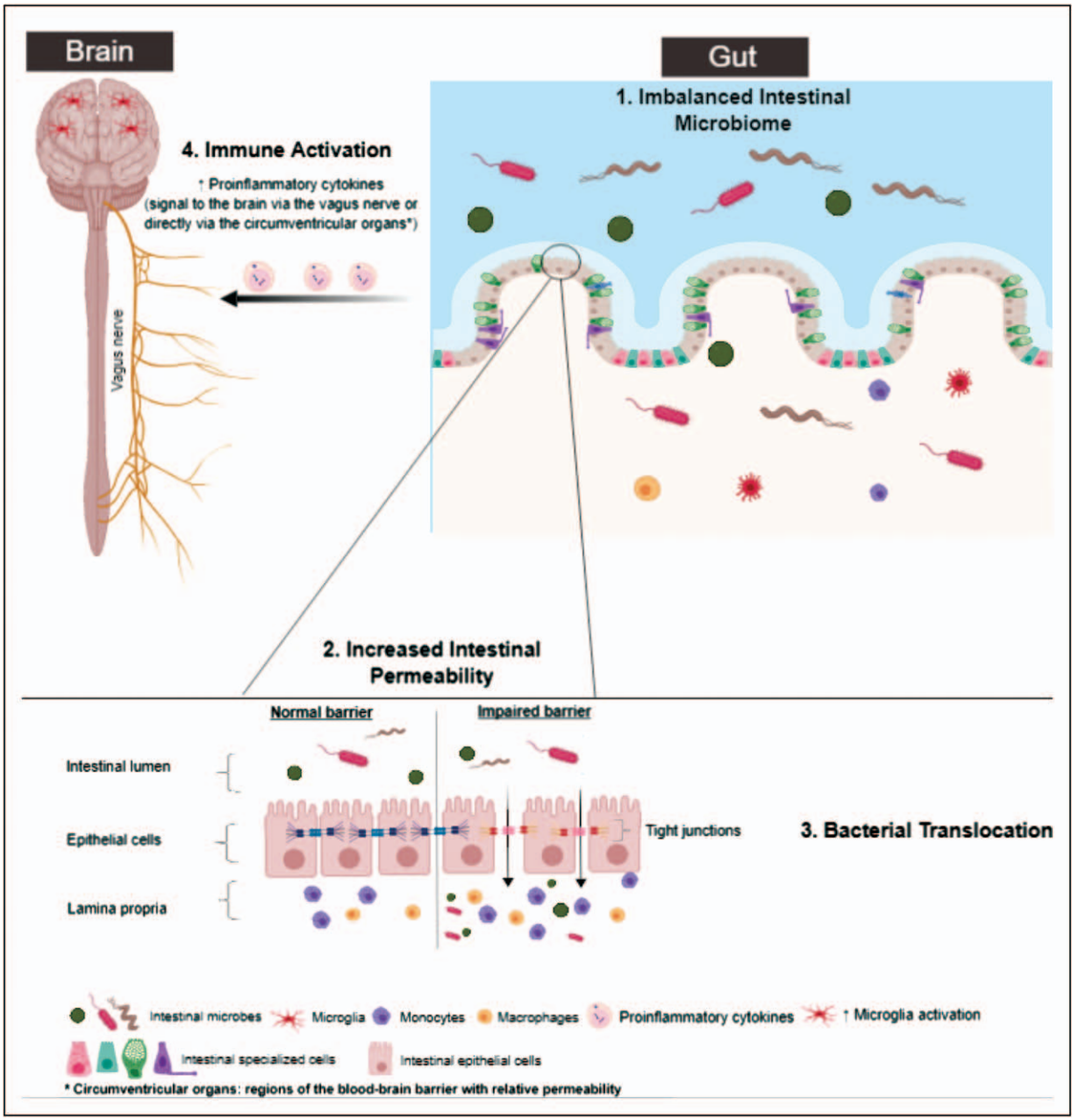

FIGURE 1. Overview of the gut-derived immune activation leading to neuronal inflammation in schizophrenia and bipolar disorder patients. (1) Different pathogens and/or microbial dysbiosis can impair tight junction via myosin light chain II phosphorylation and perijunctional actomyosin ring contraction. Impaired tight junctions will result in increased intestinal permeability. (2,3) Increased intestinal permeability leads to leakage of food-derived, microbial-derived, bacterial-derived and parasitic antigens from the intestinal lumen to the systemic circulation. Leaking Gram-negative bacteria can stimulate the production of proinflammatory cytokines, such as IL-6 and IL-1b, through binding of the lipopolysaccharide component of their cell walls to Toll-like receptors (i.e. Toll-like receptor-4), expressed on monocytes, macrophages and microglia. (4) Subsequently, that activates an inflammatory response, with the production of proinflammatory cytokines and chemokines that can signal to the brain peripherally via the vagus nerve or directly via the circumventricular organs. Microglia overactivation in the brain will be an end result. This inflammatory cascade can affect the central nervous system functioning and increase the symptom severity in psychiatric disorders.

sample size, not considering several factors such as psychotropic drug use, differences in nutrition and lifestyle behaviours between the groups, comorbid illnesses and their effect on the intestinal microbiome. Furthermore, the cross-sectional design restricted the ability to test the causality between

Table 1. Clinical trials on gut microbiome dysbiosis in patients with schizophrenia and bipolar disorder

Reference	Sample size	Mean age (SD)	Sex (M/F)	Changes in taxonomic composition (in PT compared with NC)	Association with clinical features	Limitations
Nguyen *et al.* [27▪▪]	SCZ: 25 NC: 25	SCZ: 52.9 (11.2) NC: 54.7 (10.7)	SCZ: 11/14 NC: 10/15	Phylum level: ↓*Proteobacteria* Genus level: ↑*Anaerococcus* ↓ *Haemophilus*, *Sutterella* and *Clostridium*	Greater severity of depressive symptoms was correlated with greater abundance of genus *Bacteroides* ($r=0.70$; $P=0.0002$) Increased negative symptoms were associated with decreased abundance of family *Ruminococcaceae* ($r=0.74$; $P=0.0002$) Overall self-reported mental well being was positively correlated with phylum *Verrucomicrobia* ($r=0.63$; $P=0.002$)	Cross-sectional Small sample size Comorbid medical illnesses (e.g. diabetes, hypertension), which can cause microbial differences, were not taken into consideration
Shen *et al.* [28]	SCZ: 64 NC: 53	SCZ: 42 (11) NC: 39 (14)	SCZ: 36/28 NC: 35/18	Phylum level: ↑ *Proteobacteria*, *Fusobacteria* Genus level: ↑ *Succinivibrio*, *Megasphaera*, *Collinsella*, *Clostridium*, *Klebsiella* and *Methanobrevibacter* ↓ *Blautia*, *Coprococcus and Roseburia*	Several metabolic pathways differed significantly between NC and SCZ cohorts: vitamin B6, fatty acid, starch and sucrose, tryptophan, cysteine, methionine and linoleic acid metabolism, as well as the degradation of some xenobiotics	Cross-sectional Small sample size Limited population (only Chinese Han nationality) They did not, completely, eliminate the effect of antipsychotics on the gut microbiome
Coello *et al.* [33]	BD: 113 UR: 39 NC: 77	BD: 31 (26–39) UR: 28 (22–34) NC: 29 (24.5–40.5)	BD: 43/70 UR: 18/21 NC: 30/47	Phylum level: N/A Genus level: *Flavonifractor* was present in 61% of patients with BD, 42% of their unaffected relatives and 39% of healthy individuals. In BD PTs, that was associated with smoking and female sex	N/A	Cross-sectional Small UR sample size Self-reported physical activity No dietary information No information on bowel movements or stool consistency
Painold *et al.* [35]	BD: 32 NC: 10	BD: 41.3 (14.7) NC: 31.4 (7.6)	BD: 18/14 NC: 4/6	Phylum level: ↑ *Actinobacteria* and *Coriobacteria* (class) Genus level: ↓*Ruminococcaceae* and *Faecalibacterium*	Negative correlation between microbial alpha-diversity and illness duration in BD ($R=-0.408$, $P=0.021$) Identified bacterial clades associated with inflammatory status, serum lipids, TRP, depressive symptoms, oxidative stress, anthropometrics and metabolic syndrome in individuals with BD The phylum *Actinobacteria* (LDA = 4.82, $P=0.007$) and the class *Coriobacteria* (LDA = 4.75, $P=0.010$) significantly more abundant in BD PTs compared with NC. *Ruminococcaceae* (LDA = 4.59, $P=0.018$) and *Faecalibacterium* (LDA = 4.09, $P=0.039$) more abundant in NC compared with BD	Cross-sectional Small sample size All BD in-patients in an acute episode of bipolar depression which may influence microbial diversity (stress associated by relapse, need of higher doses of medication and polypharmacy, lifestyle changes due to hospital admission; diet, physical activity, smoking habits, sleep quality) -No explicit assessment/ standardization of diet /lifestyle parameters

Table 1 (*Continued*)

Reference	Sample size	Mean age (SD)	Sex (M/F)	Changes in taxonomic composition (in PT compared with NC)	Association with clinical features	Limitations
Schwarz *et al.* [36]	FEP: 28 NC: 16	FEP: 25.9 (5.5) NC: 27.1 (6.0)	FEP: 16/12 NC: 8/8	Families: FEP ↑ *Lactobacillaceae, Halothiobacillaceae, Brucellaceae* and *Micrococcineae*, ↓ *Veillonellaceae* Genera: FEP ↑ *Lactobacillus, Tropheryma, Halothiobacillus, Saccharophagus, Ochrobactrum, Deferribacter and Halorubrum* ↓ *Anabaena, Nitrosospira and Gallionella*	*Lachnospiraceae, Bacteroides* spp., *Lactobacillus* correlated with increased psychotic symptoms. *Lachnospiraceae, Bacteroides* spp., and predominant bacteria identified by the authors *Lachnospiraceae* (*Eubacterium rectale* group), *Ruminococcaceae* (*Clostridium leptum* group), *Bacteroides* spp., *Atopobium* group, *bifidobacteria, Lactobacillus*-group (genera *Lactobacillus, Leuconostoc, Pediococcus* and *Weissella*)	Small sample size No community-level characteristics reported (alpha and beta-diversity) A model predicting remission only used top 5 families rather than the entire population More specific information about the/examination of the impact of AP medication use
Evans *et al.* [37]	BD: 115 NC: 64	BD: 50.2 (12.8) NC: 48.6 (16.6)	BD: 32/83 NC: 24/40	Phylum level: N/A Genus level: ↓*Faecalibacterium* ↓unclassified (family level: *Ruminococcaceae*)	OTU00003 (*Faecalibacterium*) associated with improved physical health, depression and sleep quality scores; OTU00024 (*Anaerostipes*) and OTU00025 (*Ruminococcaceae* family, unresolved at genus level) associated with improved physical health, while an unclassified genus from the family OTU00022 (*Enterobacteriaceae* family, unresolved at the genus level) associated with worse physical health scores	Cross-sectional Inability to control for medication use and compliance
Flowers *et al.* [39▪]	BD on AP: 46 BD off AP: 69	BD on AP: 46.0 (12.0) BD off AP: 51.7 (13.5)	BD on AP: 12/34 BD off AP: 21/48	AP-treated PTs ↑ *Lachnospiraceae* Non-AP-treated PTs ↑ *Akkermansia* and *Sutterella*	*Akkermansia* ↓ in nonobese AP-treated PTs	Illness' duration, disease's indicators and symptom severity were not taken into consideration Comorbid medical conditions/ other metabolic biomarkers effect on microbiome needed further investigation No dietary information

↑↓ Arrows indicate an increase or decrease in relative abundance when referring to taxonomic differences. NB: All studies are arranged in a reversed chronological order (from the newest to oldest). AP, antipsychotics; BD, bipolar disorder; FEP, first episode patients; LDA, linair discriminant analysis; N/A, not available; NC, nonpsychiatric comparison control; PT, patient; SCZ, schizophrenia; TRP, tryptophan; UR, unaffected first-degree relative.

the microbiome dysbiosis and symptom severity. Another, a larger study, accessing 64 SCZ patients and 53 nonpsychiatric comparison controls, from Shen *et al.* [28] also observed significant differences, in both phylum and genus levels, in intestinal microbiome between SCZ patients and nonpsychiatric comparison controls. In addition, several metabolic pathways including vitamin B6, fatty acid, starch and sucrose, tryptophan, cysteine, methionine and linoleic acid as well as the degradation of some xenobiotics differed significantly between the healthy and SCZ cohorts. Despite several limitations that are very similar to the study mentioned above, the study managed to introduce the idea of microbiome-based diagnosis for SCZ. As they distinguished the two groups, SCZ patients and nonpsychiatric comparison controls, based on 12 – characteristic quantity of bacteria. Regarding SCZ studies, there are general inconsistencies in the presence of *Proteobacteria* and *Clostridium* as studies' outcomes. This might have arisen from the heterogeneity in sample characteristics across studies. Furthermore, the presence or absence of certain chronic diseases can affect the intestinal microbiome. Therefore, more studies with better and controlled designs are required to outline a clearer picture.

Regarding the effect of antipsychotics on the gut microbiome, a recent large-scale in-vitro study investigated the effect of more than 1000 non-antibiotic drugs on gut microbiome found that nearly all subclasses of the chemically distinct antipsychotics exhibited anticommensal activity. Moreover, similarity analysis indicated that they targeted a more similar pattern of species than what would be expected from their chemical similarity. This could mean that direct bacterial inhibition may be relevant to the mechanism of action and/or side effects of antipsychotics [29]. The impact of atypical antipsychotics on the gut microbiota has been also investigated. Olanzapine-induced weight gain was observed in both male and female rats producing an altered microbiota profile with an increase in *Firmicutes* and a decrease in *Bacteroidetes*. This impact of olanzapine in rodents is not seen in germ-free animals, supporting that the weight gain is mediated by the gut microbiota. The weight gain is also attenuated when the olanzapine is coadministered with antibiotics or prebiotics [30,31]. The impact of chronic (>12 months) and short-term use of the atypical antipsychotic risperidone on the gut microbiome of paediatric psychiatrically ill male patients was examined in a cross-sectional and prospective (up to 10 months) study. Chronic treatment with risperidone was associated with an increase in BMI and a significantly lower ratio of *Bacteroidetes: Firmicutes* as compared with antipsychotic-naïve psychiatric controls [32].

Five other studies are assessing the intestinal microbiome dysbiosis in patients with bipolar disorder in comparison with nonpsychiatric comparison controls. Most recently, a study from Coello *et al.* [33] found that the intestinal microbial community of 113 bipolar disorder patients differed from that of 77 nonpsychiatric comparison controls but not from 39 unaffected first-degree relatives. Most noticeable was an increased abundance of *Flavonifractor* in the bipolar disorder group compared with nonpsychiatric comparison subjects and unaffected first-degree relatives. However, this could be caused by the much higher prevalence of smoking among bipolar disorder patients [34]. Painold *et al.* [35] also found a decrease in abundance of *Faecalibacterium* and *Ruminococcaceae* in 32 bipolar disorder patients in comparison with 10 nonpsychiatric comparison controls. In addition to this, they found that both the phylum *Actinobacteria* and the class *Coriobacteria* were significantly more abundant in bipolar disorder compared with nonpsychiatric comparison controls. An additional study from Schwarz *et al.* [36] compared 28 first episode psychosis bipolar disorder patients with 16 nonpsychiatric comparison controls. They found multiple significant differences in multiple bacteria strains (details mentioned in Table 1). They concluded that the numbers of *Lactobacillus* were elevated in the first episode bipolar disorder patients, which correlated significantly with severity along different symptoms domains. Stronger microbiome differences also seemed to indicate poorer response up to 12 months of treatment. Study design could have been improved by adding bipolar disorder patients with long-term illness. Evans *et al.* [37] studied the gut-microbiome changes in bipolar disorder patients compared with nonpsychiatric comparison mortals and tested for relationships with burden of disease measurements. They reported that less abundance of a strain of *Faecalibacterium* was associated with improved physical health, improvement on depression scores and sleep quality scores. However, they did not take medication use into account while lithium, antidepressants and other psychopharmacology agents have been proven to have an antibiotic effect [38]. An attempt to disentangle medication and disease factors on the intestinal microbiome in BP was conducted by Flowers *et al.* [39▪] comparing two groups of bipolar disorder patients, 46 patients on atypical antipsychotics users and 69 non-users. This study found differences in abundance in *Lachnospiraceae*, *Akkermansia* and *Sutterella*. The first one was increased in the group using atypical antipsychotics and the latter two were increased in the nonatypical antipsychotics group. Common limitations are that all performed studies are cross-sectional and most have a relatively small sample

size. In addition, it is always difficult to differentiate between disease factors, medication effect and effects due to illness-related behaviour. Especially in the field of microbiome studies these factors are heavily intertwingled and cannot be isolated with current available studies. It can be concluded that there are clear differences between the microbiome of bipolar disorder patients in comparison with nonpsychiatric controls but there is a little overlap of observed differences in bacterial strains in-between studies.

In regard to the effect of psychotropics on the gut microbiome, a recent in-vitro study showed fluoxetine and escitalopram to have differential antimicrobial effects. In addition, lithium, valproate and aripiprazole administration significantly increased microbial species richness and diversity, whereas the other treatments were not significantly different from controls. At the genus level, several species belonging to *Clostridium*, *Peptoclostridium*, *Intestinibacter* and *Christenellaceae* were increased following treatment with lithium, valproate and aripiprazole when compared with the control group. Rats treated with escitalopram, venlafaxine, fluoxetine and aripiprazole exhibited an increased permeability in the ileum [31].

Oropharynx

Substantial, oropharynx microbiome changes were also reported in SCZ patients. One metagenomic study assessed the bacteriophage genomes in the oral pharynx of 41 SCZ patients and 33 nonpsychiatric comparison controls. A significant difference was found in one bacteriophage genome; *Lactobacillus phage phiadh*, what correlated with the prevalence of immunological disorders as well as with the administration of valproate [40]. *Lactobacillus phage phiadh* modulates the host bacteria level *Lactobacillus gasseri,* which has been shown to modulate the immune system, largely by alterations in the function of dendritic cells, enterocytes and other components of the innate immune system [41,42]. Another metagenomic study investigated the oropharyngeal microbiome in 16 SCZ patients and 16 nonpsychiatric comparison controls. A relatively high abundance of lactic acid bacteria was reported in SCZ patients, including species of *Lactobacilli* and *Bifidobacterium*, which have been shown to modulate chronic inflammation. A significant difference was observed in *L. gasseri* (about 400 times more abundant in SCZ compared with nonpsychiatric comparison controls) [43]. Both oropharynx and gut mediated inflammation seem to share a similar mechanism and contribute to the development of psychiatric disorders of action.

Overall, for these studies assessing the microbiome in both SCZ and bipolar disorder, a general trend can be observed of differences in commensal microorganisms between these psychiatric disorders patients and nonpsychiatric controls. These differences have been found to correlate with the severity of psychiatric symptoms. However, vast conclusions should be taken with some consideration as all studies have major differences in study design and a lot have not taken outside factors proven to be of influence in microbiome composition into account (e.g. medication, metabolic syndrome, diet and smoking).

POSSIBLE THERAPEUTIC VALUE OF PROBIOTICS IN SCHIZOPHRENIA AND BIPOLAR DISORDER

To treat dysbiosis of the microbiome and thus indirectly increased intestinal permeability probiotic supplementation could be of aid. Probiotics are defined as living microorganisms that confer health benefits to the host when administered adequately [18]. They may elicit positive immunomodulatory effects by calibrating the responses of the host's immune system against pathogens and nonpathogenic organisms. As they stimulate pattern recognition receptors, which mediate the detection of bacterial antigens, and then activate signaling cascades regulating the immune response [44]. Studies assessing the effect of probiotics on hippocampal brain-derived neurotrophic factor (BDNF) in a model of low-grade colitis (AKR mice), which was associated with decreased levels of hippocampal BDNF, showed that the abnormal behaviour was reversed. They suggest that in rats probiotics promote expression of the neurotrophin under conditions of chronic stress, inflammation and ageing, most likely by reducing microglia activation [45,46]. In addition, changes have been observed in the expression of other neurotrophic factors such as glial-derived neurotrophic factor and nerve growth factor in antibiotic-treated mice [47]. A recent study in obese-insulin resistant rats showed that hippocampal oxidative stress, apoptosis and microglial activation were significantly decreased with probiotic supplementation restoring cognitive function [48].

Another reason to consider probiotic supplementation in SCZ and bipolar disorder patients is the high prevalence of gastrointestinal symptoms. In SCZ, constipation is a prevalent symptom [49–51]. Probiotics have been shown to improve constipation in different populations but haven't yet been studied in SCZ [52–54]. Bipolar disorder, in contrast, is associated with diarrhoea and satiety, a gastrointestinal symptom for which probiotics are recognized to be efficacious [55]. Therefore, probiotics

could form a potential add-on treatment in SCZ and bipolar disorder especially in patients with increased intestinal permeability.

OVERVIEW OF CURRENT CLINICAL RESEARCH USING PROBIOTICS IN SCHIZOPHRENIA AND BIPOLAR DISORDER

Currently, there are a total of six clinical studies published in which probiotics are administered in both SCZ and bipolar disorder patients (Table 2). Out of the total six published studies, there are four targeting SCZ patients and only two targeting bipolar disorder patients.

Probiotics for patients with schizophrenia

A recent study of Okubo *et al.* [56], illustrates the potential effect of *Bifidobacterium breve strain A1* in improving anxiety and depressive symptoms in 29 patients with SCZ. However, they found this potential effect in an open-label, single-arm study so a placebo effect cannot be excluded. In another pilot study, the group of Severance *et al.* [57] found that the administration of probiotics in patients with SCZ significantly helped normalize *Candida albicans* antibody levels and *C. albicans*-associated gut discomfort in 22 male individuals. In a study by Tomasik *et al.* [58] 47 immune-related serum proteins were measured in 57 chronic SCZ patients after supplementation with probiotics. They found that probiotic add-on treatment significantly reduced levels of von Willebrand factor and increased levels of monocyte chemotactic protein-1 and BDNF, which may suggest lower intestinal permeability. In addition to this, a borderline difference in chemokine (C-C motif) ligand 5 and macrophage inflammatory protein-1 beta was found. Lastly, Dickerson *et al.* [59] did not find significant differences on the Positive and Negative Syndrome Scale (PANSS) score in a study, whereas 33 patients received probiotic supplementation and 32 received a placebo. However, patients diagnosed with SCZ in the probiotic group were less likely to develop severe bowel difficulty over the course of the trial.

Consistent is that these studies found that probiotics could possibly alleviate bowel discomfort, which is a common nuisance in SCZ. However, results of studies so far displayed limited consistency regarding reduction of psychiatric symptoms.

Probiotics for patients with bipolar disorder

Regarding clinical studies with probiotic supplementation in bipolar disorder, Dickerson *et al.* [60▪] found that probiotics are associated with a lower rate of rehospitalization in 66 patients who have been recently discharged following hospitalization for mania. The probiotic's effect was increased in individuals with elevated levels of systemic inflammation at baseline based on IgG class antibodies to the NR2 peptide fragment of the *N*-Methyl-D-aspertic acid (NMDA) receptor; IgG class antibodies to gliadin; IgG class antibodies to the Mason-Pfizer monkey virus gag protein, and IgM class antibodies to *Toxoplasma gondii*. Another recent study from Reininghaus *et al.* [61] found a significant improvement in performance concerning attention and psychomotor processing speed in 20 patients and thus hypothesized that probiotic supplementation helps individuals with bipolar disorder to improve cognitive functioning. As a single arm study design was used, any influence of a placebo effect cannot be excluded.

These studies point to probiotic supplementation alleviating bowel discomfort so more data underlining these findings will be valuable. The available results seem to hint to improved cognition in at least bipolar disorder and possibly SCZ. It would be valuable if future studies could take cognitive functioning into account, as well as subjective wellbeing and immunological/inflammatory biomarkers. For a full picture, future studies should also stratify for sex and baseline inflammation to work to individualized treatment.

Intestinal permeability

To make a precise assesment of intestinal permeability in future studies, reliable biomarkers need to be established. Several studies report that patients experiencing SCZ and bipolar disorder have abnormal reactions to food-derived antigens, indicative for increased intestinal permeability. Patients with SCZ were found to have increased IgA to gliadin, β-lactoglobulin and casein [62]. A large study of SCZ patients and nonpsychiatric comparison controls from the The Clinical Anti-psychotic Trials for intervention Effectiviness (CATIE) study demonstrated that 23.1% of patients had moderate-to-high levels of IgA to gliadin (IgA-antigliadin antibodies) compared with 3.1% in the control group [63]. In another study, patients with the recent-onset of psychosis and patients with multiepisode SCZ had increased levels of IgG and IgA antibodies to gliadin compared with controls. In this study, PANSS scores for negative symptoms correlated with casein α and β antibodies [64].

Dickierson *et al.* found that bipolar disorder patients had elevated serum concentrations of IgG to gliadin and deamidated gliadin in comparison with controls [65]. In a follow-up study, it was found

Table 2. Clinical trials on probiotic supplementation in patients with schizophrenia and/or bipolar disorder

Publication	Sample size (INT/PL)	Mean age	Sex (M/F)	Study compound (way of administration: orally)	Biomarker(s)/outcome measurements	Difference between INT and comparison groups	Association with clinical features	Limitations
Okubo *et al.* [56]	SCZ: 29	INT: 45 (16)	INT: 11/17	*Strain(s): Bifidobacterium breve* A-1 Daily amount: 10^{11} cfu Form: sachet Frequency: twice daily (w. food) Treatment time: 4 weeks	HADS, PANSS, blood test, faecal microbiome	HADS ($P=0.037$), PANSS ($P=0.004$)	Probiotic supplementation may reduce the severity of anxiety and depressive symptoms in SCZ by enhancement of gut epithelial barrier function	Short treatment duration (4 weeks) Open-label, single-arm study
Severance *et al.* [57]	SCZ: 56	INT: 44.7 (11.4) PL: 48.11 (9.6)	INT: 22/8 PL: 15/11	*Strain(s): Lactobacillus rhamnosus strain GG, Bifidobacterium animalis subs. Lactis strain Bb12* Daily amount: 10^{9} cfu (per organism) Form: tablet Frequency: once daily (w. food) Treatment time: 14 weeks	Levels of antibodies to *C. albicans* and *S. cerevisiae* PANSS, query gastrointestinal functioning	*C. albicans IgG* level in males ($P<0.001$), PANSS in seronegative *C. albicans* males ($P<0.06$)	Probiotic supplementation may lead to improvement of bowel functions due to correction of yeast overgrowth	Interpretation of study results is limited by exploratory nature and small sample sizes
Tomasik *et al.* [58]	SCZ: 57 (30/27)	INT: 44.8 (11.2) PL: 48.1 (9.2)	INT: 22/9 PL: 16/11	*Strain(s): Lactobacillus rhamnosus strain GG, Bifidobacterium animalis subs. Lactis strain Bb12* Daily amount: 10^{9} cfu (per organism) Form: tablet Frequency: once daily (w. food) Treatment time: 14 weeks	47 immune-related serum proteins	von Willebrand factor ($P=0.047$), monocyte chemotactic protein-1 ($P=0.054$), brain-derived neurotrophic factor ($P=0.063$), RANTES ($P=0.069$), macrophage inflammatory protein-1 beta ($P=0.080$)	Probiotic supplementation may improve gastrointestinal leakage control in SCZ	Open-label, single-arm study Not able to detect all targeted cytokines in clinical samples Investigated SCZ patients on stable, long-term antipsychotics, but immune modularly effect still possible A small number of immune-related serum proteins identified as significantly or borderline different between two groups
Dickerson *et al.* [59]	SCZ: 65 (33/32)	INT: 44.4 (11.0) PL: 48.1 (9.4)	INT: 23/47 PL: 19/40	*Strain(s): Lactobacillus rhamnosus strain GG, Bifidobacterium animalis subs. Lactis strain Bb12* Daily amount: 10^{9} cfu (per organism) Form: tablet Frequency: once daily (w. food) Treatment time: 14 weeks	PANSS, query gastrointestinal functioning	PANSS ($P=0.25$), gastrointestinal functioning ($P=0.003$)	Probiotic supplementation may make SCZ patients less likely to develop severe bowel difficulties	Not a detailed measurement of gastrointestinal functioning No complete history of participants' gastrointestinal symptoms and associated symptoms obtained
Dickerson *et al.* [60▪]	BD: 66 (33/33)	INT: 37.9 (11.7) PL: 33.3 (13.3)	INT: 9/24 PL: 15/18	*Strain(s): Lactobacillus rhamnosus strain GG, Bifidobacterium animalis subs. Lactis strain Bb12* Daily amount: $>10^{8}$ cfu Form: tablet Frequency: once daily (w. food) Treatment time: 24 weeks	Time to psychiatric inpatient rehospitalization, BPRS, symptom assessment (YMRS), MADRAS	Time to psychiatric inpatient rehospitalization ($P=0.017$) BPRS ($P<0.0001$), YMRS ($P<0.0001$)	Probiotic supplementation may alter clinical course following mania and lessen psychiatric symptom severity in BD	Treatment received after hospital discharge was not standardized The sample may not have fully representative of patients hospitalized for mania Effect of probiotics on gut microbiome/inflammation in CNS is not directly measured
Reininghaus *et al.* [61]	BD: 20	INT: 51.5 (11.5)	INT: 11/9	*Strain(s): Lactobacillus casei W56, Lactobacillus acidophilus W22, Lactobacillus paracasei W20, Bifidobacterium lactis W51, Lactobacillus salivarius W24, Lactococcus lactis W19, Bifidobacterium lactis W52, Lactobacillus plantarum W62, Bifidobacterium bifidum W23* Daily amount: 2.25×10^{10} cfu Form: sachet Frequency: once daily (empty stomach) Treatment time: 12 weeks	TMT-A, digit symbol test, TMT-B Digit-span-test, Mittenecker Pointing Test	Digit symbol test ($P<0.001$), TMT-B ($P<0.05$)	Probiotic supplementation may increase cognitive function in patients with BD	Open-label, single-arm study Small sample size Small cognitive test battery Medications/lifestyle changes were not taken into consideration

NB: Publications are arranged in a reversed chronological order (from newest to oldest). BD, bipolar disorder; BPRS, Brief Psychiatric Rating Scale; CNS, central nervous system; HADS, Hospital Anxiety and Depression Scale; INT, intervention; MADRAS, Montgomery-Åsberg Depression Rating Scale; PANSS, Positive and Negative Syndrome Scale; PL, placebo; SCZ, schizophrenia; TMT-A, Trial Masking Test A; TMT-B, Trial Masking Test B; YMRS: Young mania rating scale.

that patients with manic symptoms had increased baseline IgG to gliadin, which normalized after 6 months of treatment [66]. In the same study, rehospitalized patients during a 6-month follow-up period were more likely to have increased IgG to gliadin compared to at the beginning of the follow-up. Two markers of bacteria translocation, soluble CD14 (sCD14) and LPS are reliabile candidates as Severance *et al.* compared serum samples of a cohort of 141 individuals with SCZ, 75 bipolar disorder and 78 nonpsychiatric comparison controls and from a second cohort of individuals with first-episode SCZ 78 who were antipsychotic-naïve or 38 who had received antipsychotic medication. sCD14 was significantly higher in both SCZ and bipolar disorder. LPS-binding protein was higher in SCZ than bipolar disorder but there was no significant difference between nonpsychiatric comparison controls and cases. Both markers where significantly correlated with c-reactive protein [67].

CONCLUSION

Although the multiple interactions between the gut microbiota, the immune system, and the CNS have not been fully understood yet, the current data indicate that there are differences in the microbiome in both SCZ and bipolar disorder patients as compared with nonpsychiatric comparison controls. Part of these differences may be caused by medication use, other by smoking and other lifestyle factors. Correlations between microbiome quantification and symptom severity have been observed in cross-sectional studies, but no relications have been conducted thus far. Probiotic supplementation was shown not only to alleviate gastrointestinal complaints in bipolar and SCZ patients but also to reduce rehospitalization rates, improvement on cognitive tasks and potentially reducement of symptom severity. Replication of findings as well as studies investigating the predictive role of intestinal permeability biomarkers is needed. Although the term probiotic has gained substantial public attention and become part of the wider vocabulary, it is important to clarify that many commercially available strains marketed as probiotics have never been tested in clinical trials and therefore by definition would not meet the criteria of conferring a health benefit.

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Conflicts of interest

There are no conflicts of interest.

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