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The gut microbiota and mental health in adults

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A growing body of evidence point toward the bidirectional gut microbiota–brain axis playing a role in mental health. Most of this research is conducted on animals why we in this review summarize and comment upon recent studies evaluating the gut microbiome in mental health in humans. Further support for the relevance of the bidirectional gut microbiota–brain communication in mood disorders has been presented, such as the effect of probiotics on brain connectivity and mental health outcomes and pregnancy related stress on gut microbiota in the newborn child. However, the heterogeneity between studies precludes conclusions regarding differences in microbiota composition in mental disease and health and many of the studies are limited by a cross-sectional design, small sample sizes and multiple comparisons. Thus, well-designed longitudinal studies with larger sample size, accounting for confounders are needed.

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Introduction

Gut microbiota may influence brain function through neural, endocrine, and immune pathways [1]. For example, the gut microbiota may impair the integrity of the intestinal barrier. The resulting release of cytokines in turn may signal to the brain through vagal activation or signaling across the blood brain barrier. In addition, substances produced by the gut microbiota may be absorbed reaching the brain by the blood stream. The brain, in turn, may influence the gut microbiota through neuronal and endocrine pathways as well as through health behaviors.

The amount of investigations into the gut-microbiota–brain axis has escalated recently as the cost for microbiota analyses has decreased. Much of the research data available on the gut microbiota–brain axis communication and mental health sequela are derived from animal research [2]. In the present review we summarize the research advances in the field based on human research published during the last two years.

We searched for original articles and meta-analyses published 2018 and 2019 registered in PubMed until November 8th 2019. Search words included microbiota combined with brain, imaging, mental, anxiety, depression, stress disorder and bipolar disorder. Studies on multiple sclerosis, Parkinson's disease, Alzheimer's disease, epilepsy, autism spectrum disorder, case reports and studies only investigating children were not included. Only English-written manuscripts were included. In total, 43 original articles and two meta-analyses were found and included in this review, and the number of review articles was more than twice as many. The studies fell within four overarching categories: 1) brain imaging studies 2) depression 3) bipolar disorder and 4) anxiety/stress with some studies fitting into more than one category.

Brain imaging

Two randomized controlled trials investigated the effect of four-week probiotic treatment on brain activity in healthy volunteers. Participants receiving *Bifidobacterium longum* 1714TM differed from participants receiving placebo in the neural oscillations in, for example, frontal and cingulate cortex during both resting-state and after social stress and the changes observed during resting state were associated with higher self-reported vitality and reduced mental fatigue [3•]. The other trial investigated a multispecies probiotic formulation. Participants receiving probiotics reported higher positive affect (mood state) and showed differences in the BOLD (blood-oxygen level-dependent) signal pattern in response to emotional decision-making and emotional recognition memory tasks compared to participants receiving placebo [4].

Three cross-sectional studies on brain connectivity were found. Higher resting state insular functional connectivity was associated with a higher fecal bacterial microbiota diversity, as well as with lower abundance of *Bacteroides* and higher abundance of *Prevotella* [5]. High levels of fecal indole metabolites were associated with functional and anatomical connectivity of areas associated with reward and anxiety [6]. *Bacteroides*, *Parabacteroidetes* and *Escherichia* species were identified as the source of GABA and an association between resting state functional connectivity in a neural circuitry considered important

in depression and a lower abundance of *Bacteroides* in patient with major depression were found [7].

Above studies support brain imaging as a tool for investigating the link between gut microbiome and brain function with tentative support for an effect of probiotics on brain activity.

Depression

By March 2018 six studies investigating gut microbiota in relation to depression were available [8]. Since then an additional 15 studies have been published and are reviewed below. The key characteristics of these studies are summarized in Table 1.

Intervention studies

Probiotic trials

Two meta-analyses evaluated the effect of probiotics in subjects with depressive symptoms and depression. The first meta-analysis included 10 clinical trials with a total of 1349 patients and found a significant mood improvement in individuals with pre-existing depressive mood symptoms after an eight-week trial of probiotics compared to placebo [9]. The second meta-analysis included three studies and 229 patients and found an overall positive effect of probiotics on depressive symptoms in clinically depressed patients when used as a supplement to antidepressant treatment compared to antidepressant treatment alone in two of the studies [10]. One of the included studies also reported a significant decrease in depressive symptoms in patients with mild to moderate major depressive disorder (MDD) receiving probiotics (*Lactobacillus helveticus* and *B. longum*) compared to patients receiving prebiotics [11].

Two randomized controlled clinical trials that were not included in the meta-analyses further evaluated the effects of probiotics on mood in patients with depression. Chahwan *et al.* did not find an effect of a multistrain probiotics on depressive scores but patients receiving the probiotics had a greater reduction in cognitive reactivity toward sad mood compared to patients receiving placebo [12]. Further, Rudzki *et al.* found that supplementing selective serotonin reuptake inhibitors (SSRI) antidepressant treatment with probiotic *Lactobacillus plantarum* 299v improved cognitive performance compared to SSRI with placebo in depressed patients [13•]. Similarly, reduction in depressive scores, as well as 70% treatment response and 35% remission rate was noted in a group receiving supplemental probiotic (CBM588) to antidepressants compared with the group on antidepressant alone in an open-label trial in patients with treatment-resistant MDD [14].

Three trials evaluated the effect of probiotics on depressive symptoms in study populations other than patients with depression. Multispecies probiotics was found to improve impulsivity and decision-making compared to placebo, but not pain, quality of life, anxiety or depressive symptoms in a double-blind, placebo-controlled, randomized study in patients diagnosed with fibromyalgia [15]. Relatedly, a small 12-week open-labeled trial with *Bifidobacterium infantis M-63* placebo found improved mental well-being compared to placebo among patients with IBS. In the same study, lower beta diversity was associated with distress and depression and lower *Lachnospiraceae* abundance was associated with a higher depression score while patients with anxiety were characterized by elevated *Bacteroidaceae* [16]. A non-randomized open label study found that *B. infantis* M-63 given for three months improved mental well-being but not depression in individuals with IBS [17].

Taken together, the presented studies support the use of supplemental probiotics to relieve depressive symptoms, or at least improve related cognitive functions.

Fecal transplants

Two studies investigating the effect of fecal microbiota transplantation on depression scores in patients with IBS or other functional gastrointestinal disorders found fecal microbiota transplantation to alleviate depression and anxiety [18,19].

Observational studies

Case control studies

Three cross-sectional case control studies compared fecal microbiome in patients with MDD and healthy controls but results are discrepant. For example, a Taiwanese study reported that patients with MDD had an overrepresentation of phylum *Actinobacteria* and *Firmicutes* and the genus *Bifidobacterium* and *Blautia* compared to healthy controls [20]. In contrast, Huang *et al.* reported lower diversity in MDD, with lower abundance of *Firmicutes* compared to healthy controls [21]. A small metaproteomic study with age, sex and BMI matched controls found a different bacterial protein signature in MDD compared to controls, with differences in proteins belonging to glucose and amino acid metabolism. Considering the merits of this profile, the authors concluded that *Firmicutes*, *Actinobacteria* and *Lachnospiraceae* were more abundant in MDD, whereas *Bacteroidetes* and *Proteobacteria* were less abundant, in MDD compared to controls [22].

Two studies investigated gut microbiota products in relation to depression. Lower fecal levels of the bacterial metabolites short chain fatty acids (SCFA) acetate and propionic acid, but higher isocaproic acid concentrations were found in depressed compared to non-depressed Polish women [23•]. In support of the theory of inflammatory changes by means of gut permeability, an American study found that individuals with more hostile marital interactions had higher bacterial endotoxin blood

Table 1

Key characteristics of reviewed studies in depression

Authors, Year	Study design	Country of origin	Study Population	Comparison groups	Symptom Assessment	Microbiome Assessment	Conclusions
Kazemi *et al.* [11]	Randomized, Placebo controlled, double-blind trial *x 8 weeks*	Iran	*N* = 81 outpatients with mild to moderate MDD, on antidepressants for 3+ months prior *Mean age: 36.5*	**Preintervention and postintervention** A- probiotic (*Lactobacillus helveticus* (*n* = 28) and *Bifidobacterium longum*) B- prebiotic (galactooligosaccharide) (*n* = 27) C- Placebo (*n* = 26)	DSM IV BDI	Pro- and prebiotic intervention	Probiotics improved BDI scores compared to placebo in patients with MDD while prebiotics did not.
Chahwan *et al.* [12]	Randomized, Placebo controlled, triple-blind trial *x 8 weeks*	Australia	*N* = 71 participants with depressive symptoms not taking antidepressants recruited from university campus *Mean age: 36.7; 35.5, 36.0*	**Preintervention and postintervention** A-Probiotics (Ecologic®Barrier; Winclove probiotics) (*n* = 34) B-Placebo (*n* = 37) C-Non-depressed (*n* = 20)	BDI M.I.N.I. DASS-21 LEIDS-R	Probiotic intervention Fecal Microbiome (16S rRNA)	All participants had reduction in depressive symptoms postintervention with similar levels of reduction among the groups. Probiotics were associated with positive effects on cognitive reactivity compared to placebo group, especially in participants with mild/ moderate depression. Fecal microbiota remained similar in all participants pre- and postintervention regardless of group but *Ruminococcus gnavus* was positively associated with DASS depression score.
Rudzki *et al.* [13•]	Randomized, Placebo controlled, double-blind trial *x 8 weeks*	Poland	*N* = 79 depressed patients admitted to psychiatry hospital *Mean age: 39.1* versus *38.9*	**Preintervention and postintervention** A-Probiotic LP299v with SSRI (*n* = 40) B-Placebo with SSRI (*n* = 39)	DSM IV HAM-D SCL-90 PSS0 APT STAB RFFT TMT A + B CVLT	Probiotics Intervention	Supplemental probiotics to SSRI antidepressants improved cognitive performance compared to placebo but not mood or perceived stress in a depressed inpatient population.
Miyaoka *et al.* [14]	Prospective Open label trial *x 8 weeks*	Japan	*N* = 40 inpatients with treatment-resistant MDD on antidepressants *Mean age: 44.3* versus *41.9*	**Preintervention and postintervention** A- Antidepressant + CBM588 (*n* = 20) B-Antidepressant alone (*n* = 20).	HAM-D BDI BAI	Probiotic intervention	Supplemental probiotics to antidepressants improved depression compared to antidepressants alone in inpatients with treatment resistant MDD and had high treatment response) and remission rate (70 and 35%, respectively).

Table 1 (*Continued*)

Authors, Year	Study design	Country of origin	Study Population	Comparison groups	Symptom Assessment	Microbiome Assessment	Conclusions
Roman *et al.* [15]	Randomized, Placebo controlled, double-blind trial *x 8 weeks*	Spain	*N* = 31 patients with fibromyalgia *Mean Age: 55.0* versus *50.3*	**Preintervention and postintervention** A-Probiotic (*n* = 16) B-Placebo (*n* = 15)	SF-36 BDI STAI MMSE	Probiotic intervention	Depressive symptoms improved in both pre- and postintervention groups but probiotics significantly improved impulsivity and decision-making compared to placebo in patients with fibromyalgia.
Peter *et al.* [6]	Cross sectional Cohort	Austria	*N* = 48 outpatients with refractory IBS *Mean Age: 19-70*	Fecal microbiome composition and psychological distress, anxiety and depression Distress (*n* = 31) Non-distress IBS patients (*n* = 17)	HADS PSQ	Fecal microbiome (16S rRNA)	Higher beta diversity abundance of several bacteria from the phyla Proteobacteria and Bacteroidetes were found in patients with psychological distress. Strong presence of Bacteroidetes members was noted in in anxiety (families Bacteroidaceae and Rikenellaceae) and in depression (family Prevotellaceae). Depression was negatively associated with Lachnospiraceae abundance while anxiety had a positive correlation with Bacteroidaceae.
Ma *et al.* [17]	Open label non-randomized study *x 3 months*	Malaysia	*N* = 53 flood-affected individuals with IBS *Mean Age: 55.3; 58.2*	**Preintervention and postintervention** A-Probiotic *Bifidobacterium infantis*M-63 (*n* = 20) B-Controls (*n* = 30)	HADS SF-36	Probiotic interventions Hydrogen breath testing Fecal microbiome (16S rRNA)	Mental well-being was improved with probiotics versus controls. The probiotic group was noted to have a lower ratio of *Firmicutes/Bacteroidetes* compared to controls, which correlated with higher post-intervention mental score.
Huang *et al.* [18]	Open label non-randomized study	China	*N* = 30 inpatients with refractory IBS *Mean age 44.0*	**Preintervention and postintervention** Fecal Microbiome Transplant *At 1 month, 3 months and 6 months after intervention* Donors- (*n* = 5) *Mean age 20.4*	HAM-A HAM-D	FMT intervention	FMT improved depressive and anxiety symptoms at 1 and 3 months after FMT but not at 6 months. FMT responders had higher Shannon diversity index before intervention than non-responders.
Kurokawa *et al.* [19]	Open label non-randomized observational study	Japan	*N* = 17 patients with IBS or functional diarrhea or constipation *Mean age: 43.4*	**Preintervention and postintervention** Fecal Microbiome Transplant *At week 0, 1, 2, 4 after intervention* Donors- *Mean age 51.4*	QIDS HAM-A HAM-D	FMT Intervention	FMT improved depressive and anxiety scores. Depressed IBS patients had a lower Shannon diversity index at baseline compared to healthy donors and IBS patients without depression.

Table 1 (*Continued*)

Authors, Year	Study design	Country of origin	Study Population	Comparison groups	Symptom Assessment	Microbiome Assessment	Conclusions
Chung *et al.* [20]	Cross sectional Case-control study	Taiwan	*N* = 73 subjects referred by psychiatrists *Mean age: 45.8* versus *41.2*	MDD (*n* = 36) HC (*n* = 37)	DSM V SADS-L BDI BAI PSS	Fecal microbiome (16S rRNA)	Alpha diversity was similar between MDD patients and HC. Phyla *Actinobacteria* and *Firmicutes* were more abundant while *Bacteroidetes* and *Proteobacteria* was less abundant in MDD patients compared to HC. At genus level, *Bifidobacterium* and *Blautia* had relatively high abundance among MDD patients compared to controls and *Holdemania* correlated positively with anxiety and, perceived stress levels in MDD patients but not in controls. Diet was accounted for with FFQ.
Huang *et al.* [21]	Cross sectional Case control study	China	*N* = 54 patients with first episode of MDD, not on antidepressants *Mean age: 49* versus *42*	MDD (*n* = 27) HC (*n* = 27)	ICD-10	Fecal microbiome (16S rRNA)	Patients with MDD had lower alpha diversity than healthy controls. *Firmicutes* was the most significantly decreased phylum in MDD compared to HC.
Chen *et al.* [22]	Cross sectional Case control	China	*N* = 20 subjects recruited from the hospital psychiatry center at and medical exam center, respectively *Mean age: 43.9* versus *39.6*	MDD (*n* = 10) HC (*n* = 10)	DSM IV	Fecal microbiome (Liquid chromatography + mass spectrometry) (Metaproteomics)	*Firmicutes* and *Actinobacteria* were more abundant in MDD, whereas *Bacteroidetes* and *Proteobacteria* were less abundant compared to HC. Patients with MDD had greater abundance of *Lachnospiraceae* and reduced abundance of *Faecalibacterium* than HC. Sex, age and BMI did not account for the differences.
Skonieczna-Zydecka *et al.* [23•]	Cross-sectional Nested case control	Poland	*N* = 116 participants recruited using chain referral sampling method *Mean Age: 52.0*	Depressed women (*n* = 47) Non-depressed women (*n* = 69)	BDI	SCFAs (gas chromatography)	Non-depressed women had higher concentrations of all SCFAs, except for isocaproic acid, compared to depressed women. Lower acetate levels but higher isocaproic acid concentration was noted in depressed women compared to non-depressed women. Concentration of acetic, propionic, and isocaproic acids were inversely associated with severity of depressive symptoms.
Kiecolt-Glaser, *et al.* [24•]	Randomized double-blind, crossover study Secondary analyses	USA	*N* = 86 43 couples recruited from the community by advertisement *Mean age: 38.2*	**Preintervention and postintervention** with therapist guided marital problem therapy sessions	DSM IV	Endotoxin markers (sCD14 and LBP) Inflammatory markers (Serum IL-6, TNF-α, CRP)	Individuals with more hostile marital interactions and history of mood disorder were observed to have a higher LBP/sCD14 ratios than those with less hostile interactions and without mood disorders.

Table 1 (*Continued*)

Authors, Year	Study design	Country of origin	Study Population	Comparison groups	Symptom Assessment	Microbiome Assessment	Conclusions
Valles-Colomer *et al.* [25]	Cross sectional Cohort study	Belgium	*N* = 1054 volunteers from the general population in Flanders *Age not mentioned*	Fecal microbiome composition and depression	General practitioner-reported depression	Fecal microbiome (16S rRNA)	Taxa *Dialister* and *Coprococcus* was reduced in subjects with depression despite adjusting for antidepressants.
Heym *et al.* [26]	Cross-sectional Cohort study	UK	*N* = 40 participants from the general population *Ages: 19–67*	Fecal microbiome composition and depressive symptoms	BDI Self judgement Overidentification Subscales of the self-compassion scale and empathy	Fecal microbiome (Only Bifidobacterium; Lactobacillus spp. evaluated, using flow cytometry)	Abundance of *Lactobacillus spp*. correlated directly with positive self-judgement but indirectly, through self-judgement, to cognitive depression and lower affective empathy.
Humbel *et al.* [27]	Cross-sectional Swiss IBD Cohort study	Switzerland	*N* = 171 IBD patients from the Swiss IBD cohort in *remission and without* stomas or colectomy *Median Age: 48*	Mucosal adherent gut microbiome composition and psychological outcomes	HADS PSQ SF-36	Mucosal adherent gut microbiome (Colon biopsies) (16S rRNA)	IBD patients in remission with self-reported higher perceived stress were observed to have lower alpha diversity compared to those with lower perceived stress. Depression was negatively associated with relative abundance of several taxa within the *Firmicutes* phylum, in both Crohn's disease and ulcerative colitis. Anxiety was only negatively associated with abundance of taxa in Crohn's disease and the phylum *Fusobacterium* was significantly decreased with increasing anxiety.
Hugerth *et al.* [28]	Cross-sectional random population-based colonoscopy study	Sweden	*N* = 375 participants from a general urban population *Mean age: 52*	Mucosal adherent gut microbiome composition and psychological outcomes	HADS SF-36	Mucosal adherent gut microbiome (Colon biopsies) (16S rRNA)	Lower diversity was associated with poorer self-rated health but not with anxiety or depression. Higher abundance of *Coprococcus catus* was associated to lower depression scores.
Taylo *et al.* [29]	Cross-sectional cohort study	USA	*N* = 133 participants without mood disorder recruited from university campus via advertisement *Ages: 25–45 years*	Fecal microbiome composition, diet and mood	DASS 42	Fecal Microbiome (16S rRNA)	Gender and dietary fiber intake affect mood and the gut microbiota. Inverse associations were noted between anxiety scale scores and Bifidobacterium in females and between depression scale scores and *Lactobacillus* in men.
Schreiner *et al.* [30•]	Cross-sectional Swiss IBD Cohort study	Switzerland	*N* = 1254 IBD patients from the Swiss IBD Cohort Study *Median Ages: 29.6 (non-vegetarians)* versus *28.1 (vegetarians)*	Mucosa-associated intestinal microbial composition, diet and psychometric outcomes	SF-36	Mucosal adherent gut microbiome (Colon biopsies) (16S rRNA)	Vegetarian IBD patients had lower mental SF-36 scores and higher level of post-traumatic stress symptoms. Significant differences in mucosa-associated gut microbiota composition was noted between vegetarian and gluten free IBD patients compared to IBD patients without diet restrictions.

Table 1 (*Continued*)

Authors, Year	Study design	Country of origin	Study Population	Comparison groups	Symptom Assessment	Microbiome Assessment	Conclusions
Liskiewicz *et al.* [31]	Clinical Trial *x 6 weeks*	Poland	*N* = 17 patients admitted to Psychiatric Hospital for depression *Mean Age: 42.5*	Inpatient hospital treatment including escitalopram administration	DSM IV	Fecal microbiome (16S rRNA)	Increased alpha biodiversity in fecal microbiota was noted after a six-week hospitalization treatment but causality in relation to patients' mental health was not investigated.

16S rRNA = 16S ribosomal RNA gene sequencing; APT = Attention and Perceptivity Test; BDI = Beck Depression Inventory; CRP = C-Reactive Protein; CVLT = California Verbal Learning Test; DASS-21 = Depression Anxiety Stress Scale; DSM IV/V = 4th edition/5th edition Diagnostic and Statistical Manual of Mental Disorders; FFQ = Food Frequency Questionnaire; HADS = Hospital Anxiety and Depression Scale; HAM-A = Hamilton anxiety rating scale; HAM-D = Hamilton Depression rating scale; HC = Healthy controls; IBD = Inflammatory Bowel Disorder; IBS = Irritable Bowel Syndrome; ICD = International Classification of Diseases; IL-6 = Interleukin-6; LEIDS-R = Leiden Index of Depression Sensitivity-Revised; LBP = LPS Binding Protein; LPS = Lipopolysaccharides; MDD = Major Depressive Disorder; M.I.N.I. = Mini-International Neuropsychiatric Interview; MMSE = Mini Mental State Examination; PSQ = Perceived Stress Questionnaire; QIDS = Quick Inventory for Depressive Symptoms; RFFT = Ruff Figural Fluency Test; SADS-L = Schedule for Affective Disorders and Schizophrenia Lifetime; sCD14 = soluble CD14; SCL-90 = Symptom Checklist; PSS = Perceived Stress Scale; SSRI = selective serotonin reuptake inhibitor (antidepressant); STAB = Stroop Test parts A and B; STAI = State-Trait Anxiety Inventory; TMT A + B = Trail Making Test A + B; TNF-α = Tumor Necrosis Factor Alpha.

levels compared to those less hostile, in particular those with a history of mood disorder [24•].

Cohort studies

In the Flemish Gut Flora Project including 1054 subjects, fecal *Dialister* and *Coprococcus* spp. were depleted in depression, even after correcting for any confounding effects of antidepressants [25]. Heym *et al.* studied 40 participants from the general population in UK and found that the fecal abundance of *Lactobacillus* spp. was directly related to positive self-judgment but only indirectly to cognitive depression and lower affective empathy [26]. Two studies have investigated mucosa associated microbiota: In a Swiss cohort study higher depressive, anxiety and stress symptoms were associated with lower microbiota diversity in 171 patients with inflammatory bowel disorder (IBD) in remission [27]. In a Swedish population-based colonoscopy study evaluating 375 participants randomly selected from the general adult population, decreased diversity was associated with poorer self-rated health, but was not associated with anxiety or depression. However, several taxonomic groups were correlated to depression and self-rated health, including *Coprococcus* [28].

Two studies highlight the importance of diet for both gut microbiota composition and mental health. In adults without mood disorders, higher anxiety and lower fecal *Bifidobacterium* was associated in women and higher depression scores and lower *Lactobacillus* was associated in men. Importantly, an inverse association was noted between the total fruit and dairy ingestion and depression and stress scores, respectively [29]. In a study on IBD patients, an association between vegetarian diet and gluten free diet and higher levels of anxiety and depression symptoms was found, while the micobiota composition in patients following a vegetarian and gluten free diet differed significantly from that of omnivores, although the direct association between gut microbiota and mental health was not investigated [30•].

In a small prospective observational study, Liskiewicz *et al.* found an increased fecal bacteria alpha biodiversity but no difference in abundance after a six-week inpatient treatment with SSRIs [31]. All patients achieved clinical improvement but the association between change in microbiome composition and the clinical course of depression was not investigated.

Overall the presented observational studies support an altered gut microbiome in subjects with depression and depressive symptoms. The specific gut microbiome composition linked to depression however varies among studies likely due to differences in study populations, methodology and presence of confounding factors.

Table 2

Key characteristics of reviewed articles in bipolar disorder

Authors, Year	Study Design	Country of origin	Study Population	Comparison	Psychometric	Microbiome measurement	Results
Coello *et al.* [38•]	Cross sectional Case Control *(age and sex matched)*	Denmark	$N = 190$ subjects recruited from the Copenhagen Affective Disorder Clinic, invited unaffected first degree relatives to subjects with BD *Mean Age: 31* versus *28* versus *29*	BD ($n = 113$) Unaffected first degree relatives ($n = 39$) HC ($n = 77$)	DSM IV HAMD YMRS	Fecal microbiome (16S rRNA)	BD was associated with increased abundance of *Flavonifractor*, a possible oxidative stress and inflammation inducer compared to HC.
McIntyre *et al.* [34]	Cross sectional Case Control	Canada	$N = 46$ subjects recruited from Univ. Hospital-based MH outpatient clinic and HC from the local community *Mean Age: 43.5* versus *49* versus *43.8*	BD -type I ($n = 15$) BD- type II ($n = 8$) HC ($n = 23$)	DSM IV	Fecal microbiome (16S rRNA)	A lower microbiota diversity and a greater abundance of a *Clostridiaceae* OTU and of *Collinsella* was associated with BD among BD-II subjects compared to HC. Diagnosis and diet did not account for the results.
Hu *et al.* [39]	Cross sectional Case Control	China	$N = 97$ depressed BD patients and HCs *Mean Age: 24.2* versus *36.3*	BD ($n = 52$) HC ($n = 45$)	DSM IV HAMD	Fecal microbiome (16S rRNA)	In BD patients the predominant phyla include Bacteroidetes whereas the Firmicutes are in the HC group. Untreated patients had lower levels of butyrate-producing bacteria compared to treated patients.
Bengesser *et al.* [35•]	Cross sectional Cohort	Austria	$N = 32$ former inpatients or outpatients at the Department of Psychiatry of Medical University of Graz *Mean Age: 41.7*	BD ($N = 29$) BD with depression versus euthymia ($n = 13$, $n = 19$, respectively)	DSM IV HAMD	Fecal microbiome (16S rRNA)	Lower bacterial diversity and evenness was noted in BD patients with depressive symptoms compared to BD patients with euthymia.
Rong *et al.* [36]	Cross sectional Case Control *(age and sex matched)*	China	$N = 91$ Inpatients and outpatients from Shenzhen Kangning Hospital *Mean Age: 41.6, 38.4, 22.0*	MDD (n = 31) BD ($n = 30$) HC ($n = 30$)	DSM V HAMD	Fecal microbiome (Shotgun metagenomics sequencing)	No difference among the 3 groups in alpha diversity. MDD and BD groups had increased phyla *Firmicutes* and *Actinobacteria* and decreased *Bacteroidetes* and more specifically, increased *Bacteroides*, *Clostridium*, *Bifidobacterium*, *Oscillibacter* and *Streptococcus* compared to HC. At the species level, BD patients had significantly increased *Escherichia blattae DSM 4481* and *Klebsiella oxytoca* and reduced *Prevotellaceae* and *Bifidobacterium longum subsp. infantis ATCC 15697 = JCM 1222* compared to the MDD group.

Table 2 (*Continued*)

Authors, Year	Study Design	Country of origin	Study Population	Comparison	Psychometric	Microbiome measurement	Results
Painold *et al.* [37]	Cross sectional Case Control	Poland	*N* = 42 inpatients at a University Hospital *Mean Age: 41.3 years* versus *31.4*	BD (*n* = 32) HC (*n* = 10)	DSM IV HAMD BDI	Fecal microbiome (16S rRNA)	Alpha diversity is similar among groups but inversely correlated with illness duration. Depressed BD individuals showed significantly higher abundances of Enterobacteriaceae, while already healthier BD patients showed higher abundances of Clostridiaceae and Roseburia.
Aizawa *et al.* [40]	Cross sectional Case Control	Japan	*N* = 97 BD patients from Psychiatry hospital clinic and HC from the local community *Mean Age: 40.3* versus *43.1*	BD (*n* = 39) HC (*n* = 58)	DSM IV HAMD	Fecal microbiome (16S rRNA)	Similar bacterial counts were among BD patients and HC. Lactobacillus counts was associated with sleep and Bifidobacterium counts were associated with lower cortisol levels in the patients.
Reininghaus *et al.* [41]	Open label trial nonrandomized, non-placebo controlled x *3 months*	Austria	*N* = 20 euthymic individuals with BD from Medical University of Graz *Mean age: 51.5*	Pre and post intervention	DSM IV HAMD YMRS	Probiotic intervention	Probiotics were associated with improved performance in attention and psychomotor processing speed after 2 and 3 months of treatment.

16SrRNA = 16S ribosomal RNA gene sequencing; BD = Bipolar disorder, BDI = Beck Depression Inventory; DASS-21 = Depression Anxiety Stress Scale; DSM IV/V = 4th edition/5th edition Diagnostic and Statistical Manual of Mental Disorders; HAM-D 17 = Hamilton Depression score 17, HC = Healthy controls; MDD-Major Depressive Disorder; YMRS = Young Mania Rating Scale.

Bipolar disorder

Clinically, BD is characterized by alternating recurrent manic, depressive or mixed mood episodes throughout the course of disease [32]. In 2017, two studies assessing the gut microbiome in bipolar disorder (BD) had been published [33], while seven more has been published to date and are reviewed below, and their key characteristics are summarized in Table 2. The reviewed studies share similar methodology in terms of their cross-sectional case control design and fecal microbiome analysis but differ in the comparative groups used, ranging from healthy controls, first degree relatives and patients with MDD, degree of depressive symptoms in BD cases as well as microbiome analysis methodology.

Some studies have found BD to be associated with a decreased bacterial diversity when compared to healthy controls [34,35•,36] while other studies found no difference [36,37]. The results are also inconsistent in terms of predominant phyla in BD [34,36,37,38•,39]. BD patients with depressive symptoms have been found to have a less bacterial diversity compared to BD patients with euthymia [35•]. Further, findings of higher levels of fecal *Bacteroides*, *Clostridium*, *Bifidobacterium*, *Oscillibacter* and *Streptococcus* when comparing individuals with BD with depressive symptoms, MDD and healthy controls [36] suggest depression to be a distinct factor in BD. In similar vein, depressed BD patients showed significantly higher abundances of *Enterobacteriaceae*, while already healthier BD patients showed higher abundances of *Clostridiaceae* and *Roseburia* [37]. Differences among types of BD, in terms of degree of mania, were reported by Rong *et al.*; BD-II, which is characterized by milder form of hypomania than BD-I, had higher abundance of *Collinsella* relative to subjects with BD-I [36]. Microbiome differences between patients with BD and depressive symptoms versus patients with MDD, have also been reported, namely an increased abundance of *Fusobacteriaceae*, *Escherichia blattae* DSM 4481 and *Klebsiella oxytoca*, but decreased *B. longum* subsp. *infantis* ATCC 15697 = JCM 1222 [36]. Importantly, treated patients were found to have a higher abundance of *Klebsiella* and *Veillonella* compared to untreated patients. Further, illness duration was associated with lower richness [36]. Other interesting findings within the BD field include reported associations between *Lactobacillus* counts and sleep and *Bifidobacterium* counts with lower cortisol levels [40].

Only one trial on probiotics in BD had been published. An open trial investigating the effect of a multistrain probiotic in euthymic individuals with BD found improvement in attention, psychomotor processing speed and executive function [41].

In brief, studies support an overall altered gut microbiome in BD but the specific microbiome composition and role of probiotics in BD remains unclear and underexplored.

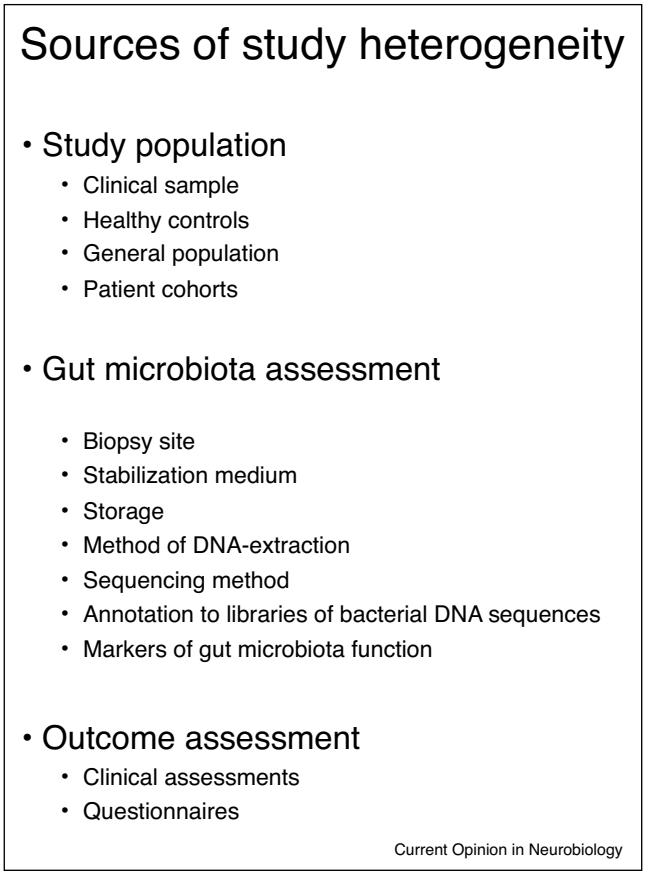
Anxiety and stress

Eight studies were found that evaluated gut microbiota and stress disorders, anxiety or adverse life events.

Two clinical trials investigating the effect of probiotics where found. In healthy young adults, a randomized controlled trial with a 4-week trial of long-term use of *Lactobacillus gasseri* CP2305 (CP2305) found improvement in mental state, sleep quality, and gut microbiota under stressful conditions by attenuating the stress-induced decline of *Bifidobacterium* spp. and the stress-induced elevation of *Streptococcus* spp. [42]. Another randomized controlled trial evaluating the effect of multispecies probiotics on anxiety in healthy college students found improvement in panic anxiety, neurophysiological anxiety, negative affect, worry, and improved negative mood regulation in the probiotic group compared to placebo group [43].

Case control studies have reported that patients with generalized anxiety disorder have lower fecal bacterial

Figure 1



The sources of heterogeneity between the reviewed studies [50].

alpha diversity, less operational taxonomic units and reduced *Firmicutes* and *Tenericutes* abundances [44] and decreased short chain fatty acid-producing bacteria and overgrowth of *Escherichia-Shigella*, *Fusobacterium* and *Ruminococcus gnavus* [45] compared to healthy controls. In addition, higher anxiety severity was associated with lower abundances of *Eubacterium coprostanoligenes* group, *Ruminococcaceae* UCG-014, and *Prevotella* 9, and higher abundances of *Bacteroides* and *Escherichia-Shigella* [44].

Veterans with combat-related post-traumatic stress disorder (PTSD) and cirrhosis had lower fecal microbial diversity, higher *Enterococcus* and *Escherichia/Shigella* and lower *Lachnospiraceaeae* and *Ruminococcaceae* compared to veterans with cirrhosis but without PTSD, and cognition was differently linked to gut microbiota in PTSD [46].

Three studies had been conducted on pregnant women. Pregnant women that reported exposure to two or more adverse childhood experiences had greater abundance of fecal *Prevotella* than pregnant women with none or only one adverse childhood experience [47]. One study investigated the hypothesis that prenatal psychosocial stress may affects child outcomes via the mother's intestinal microbiota and found an association between maternal pregnancy general anxiety and fecal microbiota composition but no associations with other stress measures included in the study [48]. Highlights among the publications is the report of an association between greater pregnancy-related anxiety and less diverse meconium microbiota community with lower abundance of the *Enterococcaceae* in the offspring [49•], supporting a causal influence of mental health on gut microbiota composition.

In summary, the reviewed studies report improved anxiety and stress symptoms with use of probiotics in healthy subjects and altered gut microbiome in patients with generalized anxiety disorder compared to healthy controls.

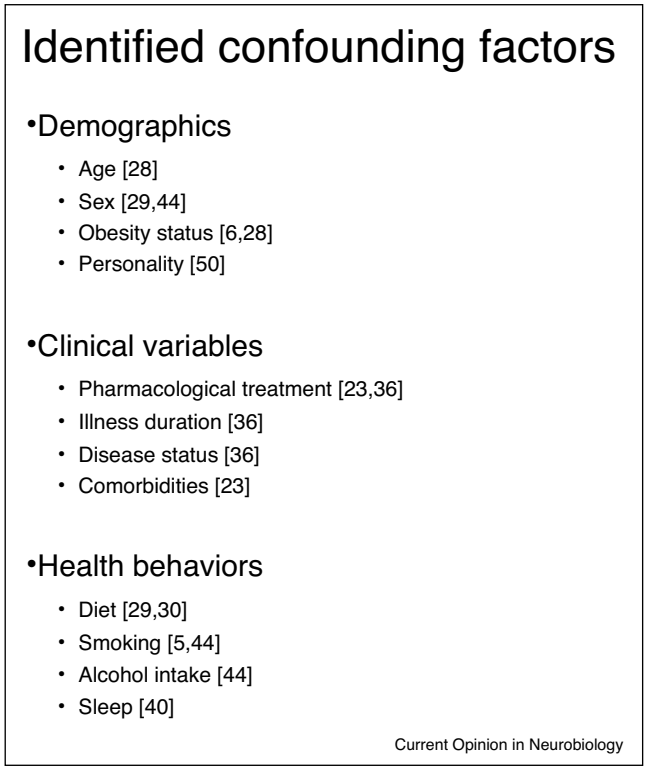
Conclusion

The human research into the gut microbiota–brain axis and mental health has accelerated during the last two years. Overall the reviewed studies provide support for the relevance of the bidirectional gut microbiota–brain communication in mood disorders in humans, such as the effect of probiotics on brain connectivity and mental health outcomes and pregnancy related stress on gut microbiota in the newborn child. However, the research is still in its early stage and studies differ in terms of study design, study populations, microbiota analyses and outcomes (Figure 1). This heterogeneity precludes conclusions regarding causality and differences in microbiota composition in mental disease and health. Importantly, this review further highlights the importance of confounding factors (Figure 2) and limitations of cross-sectional designs, small sample sizes and multiple comparisons.

Future directions

In the quest of establishing causality and clarity in gut microbiome composition and mental health status, studies with larger sample sizes, longitudinal study designs with longer follow-up periods, consistent methodology (Figure 1) and control for confounders (Figure 2) are needed. In particular, studies in BD need to account for specific factors such as type of BD, presence of depression at time of study, illness duration and treatment. Additional studies with pathway oriented approaches are needed to help elucidate the mechanistics in the gut–brain communication, such as investigations of changes in brain connectivity in response to interventions or of markers of microbiota function, for example, bacterial metabolites in feces and blood in relation to mental health status and as outcomes in interventions. Hence, we propose adding brain imaging to future studies when relevant and feasible, to increase the understanding of the gut microbiota- brain pathways and potentially provide valuable information on 'responders' versus 'non-responders' in intervention studies. Only a few studies have investigated mucosa associated microbiota in relation to mental health status. Although considerably more difficult to obtain than fecal samples, mucosal microbiota likely gives a better representation of the

Figure 2



Confounding factors identified in the reviewed studies.

organisms in premium position to influence their host and a sigmoidoscopy may be considered when a full colonoscopy would not be feasible. Importantly, the reviewed gut microbiome studies investigated the bacterial microbiota, leaving a gap in the knowledge of unicellular and multicellular eukaryotic organisms as well as archaea to be filled in the future. Of special note, the quality of the process of collecting the samples is as important as that of the microbiota analysis for the quality of the result.

Conflict of interest statement

Nothing declared.

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