




# Human Gut Microbiota and Mental Health: Advancements and Challenges in Microbe-Based Therapeutic Interventions

Helianthous Verma<sup>1</sup> · Sonika Phian<sup>1</sup> · Priya Lakra<sup>2</sup> · Jasleen Kaur<sup>3</sup> · Sanjukta Subudhi<sup>4</sup> · Rup Lal<sup>4</sup> · Charu Dogra Rawat<sup>1</sup> 

Received: 10 April 2020 / Accepted: 26 June 2020 / Published online: 7 July 2020  
© Association of Microbiologists of India 2020

**Abstract** Gut microbes play prime role in human health and have shown to exert their influence on various physiological responses including neurological functions. Growing evidences in recent years have indicated a key role of gut microbiota in contributing to mental health. The connection between gut and brain is modulated by microbes via neural, neuroendocrinal and metabolic pathways that are mediated through various neurotransmitters and their precursors, hormones, cytokines and bioactive metabolites. Impaired functioning of this connection can lead to manifestation of mental disorders. Around 1 billion of the world population is reported to suffer from emotional, psychological and neurological imbalances, substance use disorders and cognitive, psychosocial and intellectual disabilities. Thus, it becomes imperative to understand the role of gut microbes in mental disorders. Since variations occur in the conditions associated with different mental disorders and some of them have overlapping symptoms, it becomes important to have a holistic understanding of gut dysbiosis in these disorders. In this review, we consolidate the recent data on alterations in the gut microbes and its consequences in various neurological, psychological and neurodegenerative disorders. Further,

considering these evidences, several studies have been undertaken to specifically target the gut microbiota through different therapeutic interventions including administration of live microbes (psychobiotics) to treat mental health disorders and/or their symptoms. We review these studies and propose that an integrative and personalized approach, where combinations of microbe-based therapeutic interventions to modulate gut microbes and in-use psychological treatment practices can be integrated and based on patient's gut microbiome can be potentially adopted for effective treatment of the mental disorders.

**Keywords** Gut microbiota · Mental health · Microbiota-gut-brain axis · Psychobiotics · Neurological disorders

## Introduction

Human microbiome research has mushroomed over the last two decades [1] and many of its aspects are being explored to understand its implications in maintaining human health [2–4]. Microbes in the human body have potential to synthesize or modify variety of metabolites, including hormones, vitamins and other bioactive compounds that can modulate various biological functions [5, 6]. Though the exact number of microbes in the human body or number of genes in the collective human microbiome is still not fully settled [7], it is evident that the alterations in the human microbiota composition particularly in the human gut impacts human health [8]. This imbalance of the normal gut microbiota, referred as gut dysbiosis, can lead to development of diseases [5, 8]. In the quest of finding ways to restore health of an individual by bringing back the microbiota balance, the consideration of health and well-being in a holistic manner has got global attention [3, 6, 9].

✉ Charu Dogra Rawat  
cdrawat@ramjas.du.ac.in

<sup>1</sup> Molecular Biology and Genomics Research Laboratory, Ramjas College, University of Delhi, Delhi 110007, India

<sup>2</sup> Department of Zoology, University of Delhi, Delhi 110007, India

<sup>3</sup> Department of Botany, Dyal Singh College, University of Delhi, New Delhi 110003, India

<sup>4</sup> The Energy and Resources Institute, Darbari Seth Block, IHC Complex, Lodhi Road, New Delhi 110003, India

On one hand this has led to advancements towards exploring the interconnection of human with animal via ecosystem considered under ‘one health’ approach [9]. On the other hand association between microbiota and mental health that includes conditions like emotional, psychological, neurological, substance use disorders and cognitive, psychosocial and intellectual disabilities associated with them is increasingly explored.

Existence of a communication system between the gut and the mental or behavioral state (termed as gut-brain axis), has long been recognized; for instance, when we had ‘butterflies in stomach’ during nervousness or excitement or when our stomachs were ‘tied in knots’ under stress or anger or simply, when we had that ‘gut feeling’ about something. This ‘gut-brain axis’ has been implicated to be employed by the gut microbes in maintaining homeostasis in health and disease [10, 11]. Mental disorders are foremost in conferring ill-health and, worldwide, around 970 million people (~ 13% of the global population) suffer from mental disorders and disabilities [12]. Prioritizing comprehensive health as global development agenda, mental health is included in the United Nations’ Sustainable Development Goals (SDG) and also recognized in primacy for health policies around the world. This due global realization of the importance of mental well-being and recently discovered relationships between the gut microbiome and the brain have urged the scientists to decode its role in manifestation of psychiatric disorders, including major depressive disorder [13]. While there are several reviews linking gut microbiota with human health, recent information on their role in various mental health disorders has not been consolidated to bring out a complete view of the gut-brain nexus in the manifestation of many different mental health disorders, some of them characterized by overlapping symptoms. In this review, we critically analyze the role of the gut microbiota in neuropsychiatric disorders that leads to mental illness. We also provide some of the documented evidences for restoration of mental health by modulation of gut microbiota as an effect of therapeutic interventions including change in life style and dietary habits. Additionally, we put forth the need to develop and the status of the development of psychobiotics as microbe-based therapeutic strategies for the treatment of mental disorders.

## The Microbiota-Gut-Brain Axis

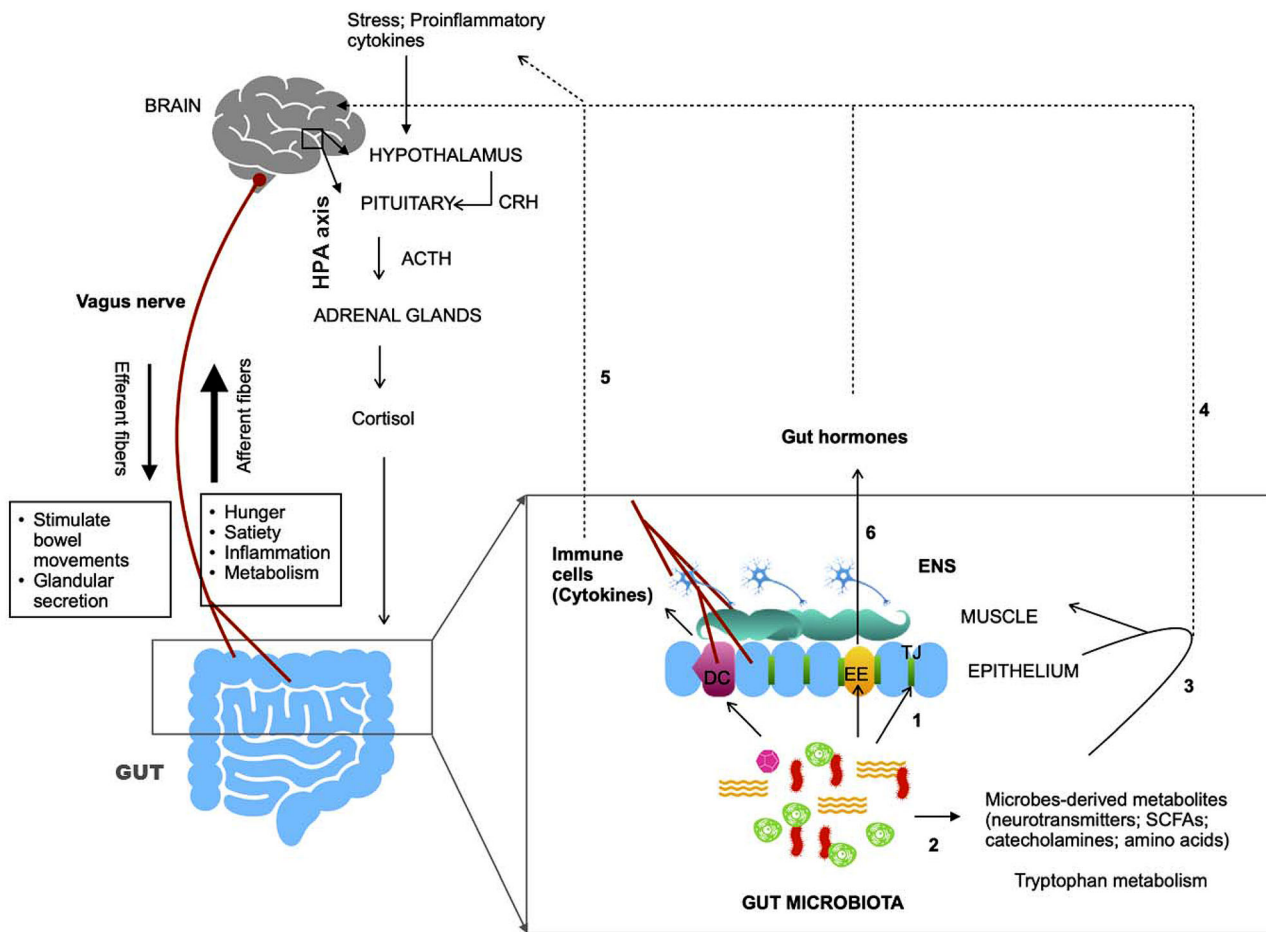
The gut-brain axis (GBA) is a bidirectional connection between a body’s central nervous system (CNS) and the enteric nervous system (ENS) [10]. Direct and indirect pathways connect emotional, memory and cognitive brain centers with the intestinal peripheral functions. A complex

crosstalk exists between the endocrine (hypothalamic–pituitary–adrenal axis), immune (chemokines and cytokines) and autonomous nervous system (ANS). All these signaling stations are involved in normal physiological functions such as permeability, secretion of hormones, production of bile salts and mucus of the gastrointestinal (GI) tract [10]. Dysregulation at any point of the network affects the GI tract homeostasis. The GBA via both its neural as well as hormonal connections allow the brain to modulate activities of the functional effector cells, such as immune cells, enteric neurons, muscle cells, epithelial cells etc. of the intestine [10]. These cells are also under the effect of the gut microbiota that, therefore, impacts the GBA [10]. The significance of gut microbiota in the regulation of the gut–brain communication has led to the broadening of the concept of GBA to the Microbiota-Gut-Brain axis [11]. Figure 1 depicts the structural and functional aspects of the Microbiota-Gut-Brain axis. As depicted in the figure, the gut microbiota communicates with brain through three major pathways—the neural pathway (vagus nerve, enteric nervous system), the immune pathway (cytokines) and the endocrine pathway (HPA axis, gut hormones). (Fig. 1). Vagus nerve via efferent fibers stimulate different gut targets to modulate gut mobility, permeability, secretion of hormones, and bowel movements. Signals for hunger, satiety, inflammation or metabolism goes to brain via afferent fibers of the vagus nerve. Vagal neurons interact with the gut neuropod cells to form synapses. Gut microbiota modulates the gut-brain axis via numerous direct and indirect ways (Fig. 1, 1–6): by helping in maintaining gut permeability by modulating the integrity of tight-junctions in the gut epithelium (1), by producing a wide variety of metabolites including neurotransmitters e.g. serotonin,  $\gamma$ -aminobutyric acid (GABA); short chain fatty acids (SCFAs) e.g. butyric acid, propionic acid; catecholamines e.g. dopamine, norepinephrine; amino acids e.g. tryptophan; secondary bile acids, D-lactic acid and gases e.g. nitric oxide, ammonia (2). Microbes-derived metabolites can affect the CNS by acting locally on ENS and vagus nerve (3) or enter circulation and affect the brain (4). Gut microbiota also act locally on gut immune cells (e.g. dendritic cells) and enteroendocrine cells and stimulate the release of cytokines (5) and hormones (6), respectively [14].

## Early Evidences of Association of Gut Microbiota and Mental Health

Revelation of microbiota-gut-brain connection led researchers to speculate the role of gut microbiota in mental health and behavior of individuals. An earlier study on germ-free (GF; no exposure to microorganism) rodents

### THE MICROBIOTA – GUT – BRAIN AXIS

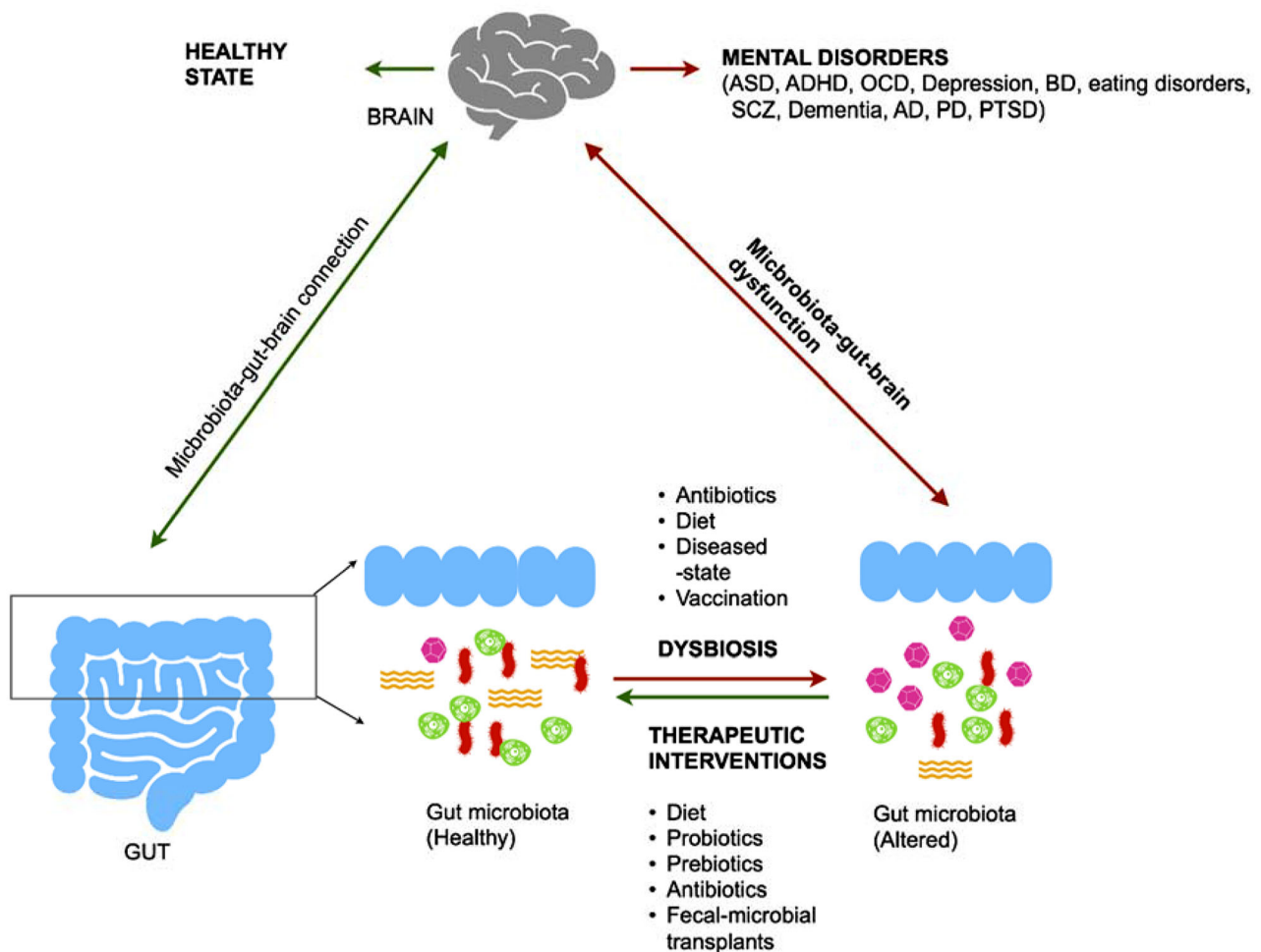


**Fig. 1** Microbiota and the gut-brain axis. The gut-brain axis forms a bidirectional network involving three major pathways—the neural pathway (vagus nerve, enteric nervous system), the immune pathway (cytokines) and the endocrine pathway (HPA axis, gut hormones). Gut microbiota modulates this axis via numerous direct and indirect

ways (1–6, as described in the text). *HPA* hypothalamic–pituitary–adrenal axis, *EE* enteroendocrine cells, *DC* dendritic cells, *TJ* tight junctions, *SCFAs* short chain fatty acids. Bold arrows: local interactions; dashed arrows: via circulation

revealed learning deficiency and impacts on anxiety behavior and sociability [15]. The role of microbiota in the modulation of brain’s neurochemical behavior was evidenced in a preclinical study on vagotomized healthy mice administered with *Lactobacillus rhamnosus* [16]. *L. rhamnosus* (JB-1) could modulate mice’s GABAergic system therefore producing beneficial effects on mental health by reducing depression-related and anxiety-like behavior [16]. Further, alteration in the levels of gut microbial metabolites, such as SCFAs, SBAs, D-lactate, ammonia, tryptophan, histamine have shown to be associated, directly or by breaking down into neuroactive catabolites (for e.g. tryptophan breaks down along kynurenine pathway to produce many catabolites that are neuroactive) with various neurological conditions like

Parkinson’s disease (PD), Anorexia Nervosa (AN), Alzheimer’s disease (AD), Autism spectrum disorder (ASD), chronic stress, depression etc.[14, 17–23]. These evidences clearly exhibited the existence of association between the microbiota-gut-brain axis and mental health and opened a way of addressing mental health disorders as a dysfunction of this axis (Fig. 2). However, whether this disruption of homeostasis in the mental health disorders is cause or effect of the alterations in gut microbiota and its functions is not emphatically clear and require more evidential studies.



**Fig. 2** Gut microbiota in mental disorders. Gut dysbiosis leads to the manifestation of several mental health disorders such as autism spectrum disorder (ASD), attention-deficit/hyperactivity disorder (ADHD), obsessive–compulsive disorder (OCD), depression, bipolar disorder (BD), eating disorders, schizophrenia (SCZ), dementia,

Alzheimer’s disease (AD), Parkinson’s disease (PD) and post-traumatic stress disorder (PTSD). Many interventional strategies targeted at restoring healthy gut microbiota through alterations in diet, probiotics, prebiotics, antibiotics and fecal microbial transplants have been suggested as potential therapeutics for these mental disorders

### Gut Dysbiosis, Mental Health Disorders and Therapeutic Interventions

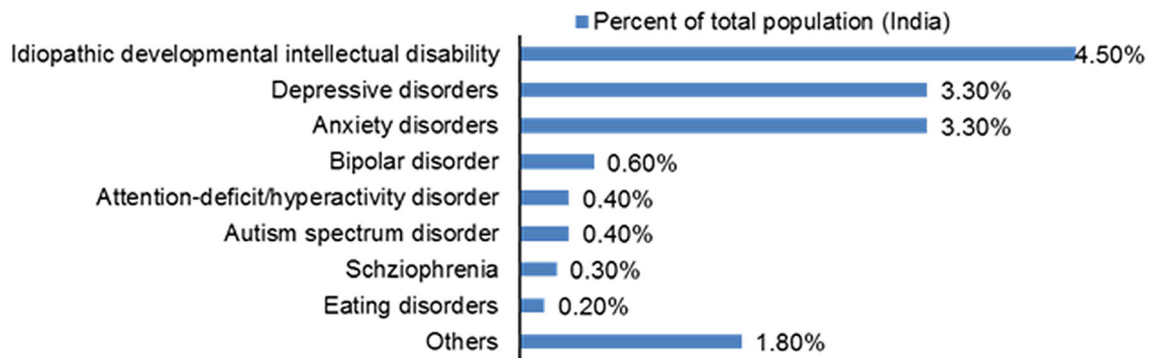
By 2017, around 197 million of people, comprising around 14% of the total population of India suffered with mental illness of one kind or another i.e. 1 in every 7 people had a mental disorder—mild to severe [24], which is almost double from the year 1990. Figure 3 depicts the burden share of various mental disorders in India.

Considering the alarming increase in the burden of mental disorders and the evidences of association that exists between the gut microbiota and mental health (discussed in the previous section), it becomes imperative to have a comprehensive understanding of the role of the gut microbiota in various mental disorders. We consolidate these studies (Table 1) that can guide us for developing suitable therapeutic interventions to mitigate the

disquieting burden of various mental disorders. Some of the employed treatment strategies and their outcomes are also included (psychobiotics are dealt later in a separate section) (Table 1).

### Neurodevelopmental Disorders

In neurodevelopmental disorders the development of CNS is impaired. Brain dysfunction can lead to imbalance in motor functions, language, learning and non-verbal communications. This can lead to Intellectual Disability (ID), earlier termed as mental retardation, Autism Spectrum disorder (ASD) and Attention-Deficit Hyperactivity Disorder (ADHD). Many microbiome research studies are focused on ASD patients [20, 25]. Disturbed GI tract in ASD patients provided the sign of possible link between the gut microbiota and ASD. Alteration in the



**Fig. 3** Burden share of various mental disorders in India [24]

Bacteroidetes/Firmicutes ratio in ASD patients is reported, although direction of change is not consistent in studies. Increased relative abundance of bacterial genera *Bacteroides*, *Barnesiella*, *Clostridium* and *Roseburia* and reduced relative abundance of *Bifidobacterium*, *Coprococcus*, *Dialister*, *Faecalibacterium*, *Prevotella*, and *Streptococcus* have been found in different cases [25]. SCFA metabolism changes affected by changes in *Faecalibacterium*, *Ruminococcus*, and *Bifidobacterium* composition has also been reported [25]. Studies have focused on Fecal Microbial Transplantation (FMT)—which include transfer of fecal microbiota from healthy donors to a patient, changing the dietary habits and use of antibiotics to reverse the gut dysbiosis and few have succeeded to an extent. For instance, children with ASD showed improved behavior and 80% reduction in GI problems after a modified FMT treatment [26]. The modified FMT treatment, Microbiota Transfer Therapy (MTT), involves antibiotics administration, a bowel cleanse, a stomach-acid suppressant followed by FMT. Increased abundance of *Bifidobacterium*, *Prevotella*, and *Desulfovibrio* was also observed after the treatment. Improvements persisted even after two years in the gut microbiota as well as in the behavior of ASD patients [26].

Significantly reduced gut microbial diversity was observed in young patients with ADHD and elevated levels of *Bacteroides* and the genus *Neisseria* was suggested to be associated with juvenile ADHD [27]. In ADHD patients, probable role of diet in controlling the intensive behavior has been suggested [28]. Gut microbiome demonstrated the predominance of Actinobacteria, especially *Bifidobacteria* in ADHD patients. In a study, where micronutrients have been given to the patients, only decline in *Bifidobacteria* population was observed which was indicative of a positive effect [28]. However, no profound effect was observed in rest of the microbial community or symptoms. These studies reflect on the importance of determining gut microbiota in neurodevelopmental disease diagnosis so that community alteration profile can be employed as a cure.

### Anxiety Disorders

Anxiety symptoms are generally observed in the patients suffering from different mental disorders. It is generally divided into Generalized Anxiety Disorder (GAD), Phobias, Panic Disorder, Social Anxiety Disorder (SAD) and Obsessive–Compulsive Disorder (OCD). Jiang et al. observed that along with decrease in richness and diversity of gut microbial community, patients suffering with GAD also showed reduction in SCFAs-producing bacteria [29]. In addition, certain genera, *Escherichia*, *Fusobacterium*, *Shigella* and *Ruminococcus*, were observed more than the normal level [29].

For the therapeutic strategies to treat anxiety disorders, among 21 studies implemented on nearly 1503 patients, 14 studies included the use of probiotic supplements to modulate intestinal microbiota while the rest of the studies focused on improving diets instead of probiotics. In these 14 studies, seven used only one type of probiotic supplement, two used two types and five used at least three types of probiotics [30]. 11 out of 21 studies showed improvement on anxiety symptoms in which five were probiotic based and six were non-probiotic based [30]. These observations indicated two points about the therapeutic strategies that can be employed for anxiety disorders; one, the non-probiotic or improvement in diet is equally effective as probiotic supplements and second, more than 50% studies (86% in case of diet regulation i.e., six out of seven), reflect that alteration in gut microbiome may be a tool for improving the anxiety symptoms.

### Mood Disorders

Mood disorders can range from mild, such as, mood swings to severe, such as, depression and bipolar disorders (BD). A recent study has shown dysregulation of the HPA axis as a result of the gut dysbiosis, to be associated with the major depressive disorder and improvements in the symptoms of depression correlated with the restoration of the HPA axis



**Table 1** Gut dysbiosis, its consequences, therapeutic interventions and their outcomes in various mental health disorders

Mental health disorder	Change in gut microbiota	Consequences of microbial dysbiosis	Therapeutic interventions	Observations after treatment/therapy	References
Autism spectrum disorder (ASD)	Alterations in Bacteroidetes/firmicutes ratio Increase abundance of <i>Bacteroides</i> , <i>Barnesiella</i> , <i>Clostridium</i> and <i>Roseburia</i> Decreased abundance of <i>Bifidobacterium</i> , <i>Coprococcus</i> , <i>Dialister</i> , <i>Faecalibacterium</i> , <i>Prevotella</i> , and <i>Streptococcus</i>	Less production of butyrate and lactate; mucin degradation	FMT Changes in diet Antibiotics	Increased abundance of <i>Bifidobacterium</i> , <i>Prevotella</i> , and <i>Desulfovibrio</i> FMT associated changes in GI and ASD symptoms	[20, 25, 26]
Attention-deficit/hyperactivity disorder (ADHD)	Increase abundance of <i>Bifidobacterium</i> <i>Neisseria</i>	Predicted enhanced biosynthesis of cyclohexadienyl dehydratase—enzyme required for dopamine synthesis	Micronutrient supplementation	Decline in abundance of <i>Bifidobacterium</i>	[27, 28]
General anxiety disorder (GAD)	Increase abundance of <i>Fusobacterium</i> , <i>Ruminococcus</i> and <i>Escherichia-Shigella</i> Decrease in SCFAs-producing genera— <i>Faecalibacterium</i> , <i>Eubacterium</i> and <i>Sutterella</i>	Immune activation Degradation of mucin	Non-probiotic (supplementary of the resistant dextrin)	Improvement in anxiety symptoms	[29, 30]
Depression	Abundance of <i>Prevotella</i> , <i>Klebsiella</i> , <i>Enterobacteriaceae</i> and <i>Alistipes</i> Decrease in <i>Faecalibacterium</i> , <i>Coprococcus</i> , <i>Dialister</i> , <i>Ruminococcus</i> species <i>Lachnospiraceae</i> family <i>Lactobacillus</i> and <i>Bifidobacterium</i> species	Butyrate production decline Increased intestinal inflammation	FMT—capsule administration	Reduction in the psychological distress	[31, 32]
Bipolar disorder (BD)	Increase in Bacteroidetes, Actinobacteria, class Coriobacteria, <i>Lachnospira</i> , <i>Enterobacteriaceae</i> , <i>Flavonifractor</i> Decrease in Firmicutes Butyrate producing genera— <i>Roseburia</i> , <i>Faecalibacterium</i> and <i>Coprococcus</i> , <i>Ruminococcaceae</i>	Reduction in butyrate production Abnormal glucose metabolism Oxidative stress	Special nutritional diet Pharmacotherapies including lithium, anticonvulsants, and atypical antipsychotics (AAP)	Improvement in the symptoms of the disease	[32–36]
Schizophrenia (SCZ)	Increase in <i>Lactobacillus</i> <i>Streptococcus vestibularis</i> , <i>Lactobacillus fermentum</i> , <i>Enterococcus faecium</i> , <i>Alkaliphilus oremlandii</i> , and <i>Cronobacter sakazakii</i> <i>Cronobacter turicensis</i> Decrease in <i>Veillonellaceae</i> <i>Lachnospiraceae</i> and <i>Ruminococcaceae</i> family, Proteobacteria, Firmicutes, <i>Clostridia</i> , <i>Haemophilus</i> , <i>Sutterella</i>	Reduction in mucin, SCFAs Immune activation and neuroinflammation	Fiber rich diets suggested as an effective treatment FMT- capsule administration	Improved social-behaviors	[36–38]

**Table 1** continued

Mental health disorder	Change in gut microbiota	Consequences of microbial dysbiosis	Therapeutic interventions	Observations after treatment/therapy	References
Anorexia nervosa (AN)	Abundance in Firmicutes, <i>Methanobrevibacter smithii</i> Reduction in <i>Bacteroides</i> <i>Roseburia</i>	Reduction in butyrate Production of autoantibodies leads to cross reactivity with host neuro-peptides and hormones Decrease in appetite and food efficiency	FMT (in GF-mice and AN patients)	Increase in Bacteroidetes Improvement in compulsive behavior	[39, 40]
Addiction (Substance abuse)	Abundance in Bacteroidetes, Proteobacteria, Fusobacteria, <i>Bacillaceae</i> and <i>Ruminococcaceae</i> , <i>Enterococcaceae</i> and <i>Staphylococcaceae</i> <i>Paracoccus</i> , <i>Thauera</i> , and <i>Prevotella</i> species	Neuroinflammation and gut inflammation	Antibiotic administration (in normal mice)	Enhanced sensitivity towards cocaine rewards	[42]
Post-traumatic stress disorder (PTSD)	Abundance in <i>Enterococcus</i> and <i>Escherichia-Shigella</i> Decrease in Actinobacteria, Lentisphaerae, and Verrucomicrobia, <i>Lachnospiraceae</i> and <i>Ruminococcaceae</i>	Decreased immunoregulation	FMT Diet change	Reduction in severity of PTSD	[43, 44]
Dementia	Increase in Firmicutes/bacteroidetes ratio Decrease in Bacteroidetes	Lower cognitive function	Probiotics	Alleviated cognitive dysfunction by modulating CNS functions	[47]
Alzheimer's disease (AD)	Abundance in <i>Escherichia</i> and <i>Shigella</i> Reduction in <i>Eubacterium rectale</i>	Production of proinflammatory cytokines Alteration in neurotransmitters level	Antibiotics	Use of antibiotics Reduced inflammation but sometime with side effects	[48]
Parkinson's disease (PD)	Abundance of <i>Bifidobacteriaceae</i> , <i>Lactobacillaceae</i> , <i>Pasteurellaceae</i> , <i>Christensenellaceae</i> , <i>Lachnospiraceae</i> and <i>Verrucomicrobiaceae</i> Reduction in <i>Lachnospiraceae</i>	Depletion in SCFA results in inflammation in brain and colon, constipation Mucin degradation	Drugs	Reduction in disease symptoms with side effects Improvement in the disease symptoms	[49, 50]

[13]. In another study, population of *Faecalibacterium* and *Coprococcus*—butyrate producing organisms and of *Dialister* were observed declining in patients suffering from depression [31]. This study also supported a connection of dopamine production and gut microbiota as 3,4-dihydroxyphenylacetic acid, a metabolite of dopamine is correlated with mental health of the patients. Many studies have indicated that both the microbiota diversity and richness declined in patients suffering from major depressive disorder when compared to the healthy controls [32]. On the genus level, the abundance of *Prevotella*, *Klebsiella*, *Enterobacteriaceae* and *Alistipes* increased, while the abundance of family *Lachnospiraceae* (SCFA producers) and genus *Faecalibacterium* and *Ruminococcus*

decreased [32]. The decrease in the abundance of gut-beneficial bacteria, *Lactobacillus* and *Bifidobacterium* was also observed in the depression patients [32]. The association between gut microbiota and BD has been revealed that indicated the abundance of Actinobacteria and class Coriobacteria and decline in *Faecalibacterium* and *Ruminococcaceae* in BD patients [32]. Also, the family *Clostridiaceae* and genus *Roseburia* were abundant in healthier BD patients compared to depressive patients which showed more members of family *Enterobacteriaceae*. Change in the gut microbiota in BD patients may also relate with increased risk of metabolic changes. For instance, *Flavonifractor* abundance in BD patients have shown to relate with oxidative stress and inflammatory

response [32]. Interestingly, both BD and major depression disorder resulted in dysbiosis in similar bacterial phyla and families such as abundant Actinobacteria, *Enterobacteriaceae* and low *Faecalibacterium*. Members of the family *Lachnospiraceae* were found reduced in patients suffering with depression while increased abundance of genus *Lachnospira* was found in the BD patients [32]. Recently, Hu et al. determined that patients with BD are likely to have more population of Bacteroidetes compared to healthy people who have more Firmicutes in their gut [33]. The study also characterized many gut microbiota-based biomarkers for diagnosis and determining outcomes for the treatment of BD.

An initial study of a 21 year old patient with both BD and ADHD showed the effect of special nutritional diet which proved remarkable in improving symptoms of the disease [34]. However, by that time, role of microbiome and gut-brain axis was not well known. Pharmacotherapies including lithium, anticonvulsants, and atypical antipsychotics (AAP) are approved for the management of BD and many studies have explored the interaction between the drugs used and the gut microbiota [35]. FMT improved by capsule administration has been shown to be likely to strongly improve the microbiota-oriented treatments in major depression and schizophrenia (SCZ) [36].

### Psychotic disorders

Psychotic mental disorder patients can not differentiate between reality and imagination and undergo hallucinations, one such example is schizophrenia (SCZ). Studies investigating microbiome differences between SCZ patients and healthy individuals have given inconsistent results with *Anaerococcus* and *Bacteroides* were found increased and taxa under Proteobacteria, *Clostridia*, *Haemophilus*, *Sutterella* were found significantly reduced in SCZ [37]. *Lactobacilli* is only found to be consistently significantly elevated in SCZ and in people with increased risk of SCZ and even correlated with the severity of the SCZ symptoms. Reduced alpha-diversity was noted in SCZ patients and bacterial taxa such as *Veillonellaceae* and *Lachnospiraceae* were found to be associated with the gut of SCZ patients [37]. Metagenome-wide association study (MWAS) on 90 medication-free SCZ patients and 81 controls has delineated differences in SCFAs synthesis, tryptophan metabolism, and synthesis or degradation of neurotransmitters as functional potentials associated with SCZ [38]. *Streptococcus vestibularis*, *Lactobacillus fermentum*, *Enterococcus faecium*, *Alkaliphilus oremlandii*, and *Cronobacter sakazakii/turicensis* were found to be enriched in the SCZ gut [38].

Microbiome targeted treatments have not been well-studied yet in SCZ patients, however as stated above

FMT improved by capsule administration has shown potential to improve the microbiota-oriented treatment [36]. Also, use of pre/probiotics have shown to be promising auxiliary treatments in SCZ [38]. For instance, transplantation of *Streptococcus vestibularis* into antibiotic-based microbiota depleted mice appeared to induce deficits in social behaviors, and was found to alter the neurotransmitter levels in peripheral tissues in recipient mice [38].

### Eating And Addiction Disorders

Of the three major eating disorders—Anorexia Nervosa (AN), Binge Eating Disorder (BED) and Bulimia Nervosa (BN), association of AN with gut microbiota has gained attention. Roots of AN are also found associated with gut dysbiosis and low gut microbial diversity. Levels and affinities of gut microbiota-produced neuroactive compounds were found to be associated with eating disorders [17]. In the acute stages of AN, phylum Bacteroidetes were found to be reduced and Firmicutes were increased [39]. Furthermore, in AN patients the genus *Methanobrevibacter* and specifically, *M. smithii*, was found to be increased while the *Roseburia* species decreased [39]. Fecal transplants from the AN patients into GF mice has shown the development of AN-like behavior in the recipients [40]. This includes dysbiosis, reduced appetite, low rate of weight gain and increased compulsive behavior. Also, serotonin levels were found to be lower as compared to normal healthy mice. Administration of *Bacteroides vulgatus* has shown improvement in compulsive behavior but did not help in the weight gain [40].

Addiction mainly includes addiction to alcohol or substance use. The link between the gut microbiota and alcohol addiction has been established suggesting gut-inflammation, neural inflammation and change in microbiota.[41]. *Lactobacillus*, *Bifidobacterium* or *Akkermansia* have shown to enhance intestinal integrity and maintain the gut barrier in alcohol-use disorder patients [41]. Patients with substance abuse have also shown a sign of change in gut-microbial community. Cocaine use disorder showed increased relative abundance of Bacteroidetes. Increased relative abundance of several taxa from Proteobacteria and Fusobacteria phyla have been observed in the rats administered with the psychostimulant, methamphetamine (also known as ice). *Bacillaceae* and *Ruminococcaceae* within Firmicutes phyla were more abundant in the ice-administered mice. Reduction in Bacteroidetes/Firmicutes ratio has also been observed in the morphine-treated rodents, with expansion of potentially pathogenic bacterial families such as *Enterococcaceae* and *Staphylococcaceae*. *Thauera*, *Paracoccus* and *Prevotella* have also been identified as substance-related bacteria [42]. Experiments have



been performed to show the relation of substance use and behavioral patterns. One such study involved reducing the gut microbiota of normal mice by administering antibiotics orally. This resulted in enhancing the sensitivity towards cocaine rewards in antibiotic-treated mice as compared to antibiotics-untreated mice [42], suggesting that the altered microbiota can enhance the response to such addictions. Although gut dysbiosis is implicated in eating and addiction disorders, more mechanistic studies utilizing antibiotics or FMT are warranted.

### Stress Related Disorders

Stress affects body homeostasis and body's response includes headache, depression, anger and anxiety which relates with change in gut microbiota, immune system function and gut motility. Stress might also be the basis of many CNS disorders discussed above. Post-traumatic stress disorder (PTSD) patients have been shown to possess similar gut-microbiota as stressed individuals but showed the decrease in Actinobacteria, Lentisphaerae, and Verrucomicrobia populations. Poor cognitive performance was observed in PTSD veteran patients with cirrhosis. This was marked with lower gut microbial diversity in PTSD with higher *Enterococcus* and *Escherichia/Shigella* and lower beneficial taxa belonging to *Lachnospiraceae* and *Ruminococcaceae* [43]. Recently, Xu et al. have shown alteration in the relative microbial abundance post stress conditions in rats. The stress-induced differences disappeared in adolescents, however, persisted in adults [44]. They also identified significantly altering metabolites correlated with correlated gut microbes that can be further explored for their therapeutic potential for the treatment of stress disorders [44]. FMT or dietary changes may also help in altering the severity of PTSD [43].

Another disorder linked with stress and anxiety is characterized by inability to sleep properly such as insomnia which is identified as the most prevalent sleep disorder. Gut microbiota and serotonin production are linked, as 90% of serotonin is produced by chromaffin cells in GI tract and spore forming bacteria in gut controls the release of serotonin from these cells. Also, *Escherichia coli* and species of *Enterococcus* secrete small amounts of serotonin [45]. Along with serotonin, other neurotransmitters like dopamine, GABA and melatonin, produced by gut microbes, have profound effect on sleep quality and circadian misalignment. It is also observed that the inflammatory reactions due to gut microbiome dysbiosis may lead to affect normal immune system and can influence CNS to cause insomnia-type conditions [45].

### Neuro-cognitive Disorders

Neuro-cognitive disorders include delirium that involve confused thinking and less awareness about the things happening in the surroundings. Abdominal surgeries of mice model has shown that change in gut microbiota increased the occurrence of delirium condition [46]. Dementia is another neuro-cognitive disorder linked with reduced memory, language ability and problem solving and understanding abilities. It is a primary condition associated with Alzheimer's disease (AD). Terminal-Restriction Fragment Length Polymorphism (T-RFLP) revealed that Bacteroidetes are declined in dementia patients than non-dementia patients [47]. Moreover, ratio of Firmicutes/Bacteroidetes is also increased in dementia patients [47]. AD has also been indicated to be associated with dysbiosis. An earlier study had demonstrated increased abundance of a pro-inflammatory taxa, *Escherichia* and *Shigella*, and reduction in an anti-inflammatory taxon, *Eubacterium rectale* in AD patients [48]. In AD, effect of antibiotics has prevalently linked changes in brain activity due to decline in gut microbial population [48]. Neuropsychiatric symptoms of anxiety, depression, apathy, sleep disorders as well as, later in the course, delirium and dementia have been associated with Parkinson's disease (PD) which is defined by impaired motor responses characterized by slow movement, rigidity and tremor. GI symptoms (such as, constipation), colonic inflammation and appearance of neuropathological hallmarks,  $\alpha$ -synuclein and Lewy bodies in the gut before they appear in brain clearly indicated linkage between gut and brain in the manifestation of the disease [49]. Hill-Burns et al. based on a case-control study conducted on 327 subjects (197 PD cases and 130 controls) concluded that PD is associated with gut microbiome dysbiosis [50]. This group studied the gut microbiome at taxonomic, functional and global levels and found significant alterations in the abundance of *Bifidobacteriaceae*, *Lactobacillaceae*, *Pasteurellaceae*, *Christensenellaceae*, *Lachnospiraceae*, and *Verrucomicrobiaceae* families and revealed modulations in many metabolic pathways including metabolism of plant-derived compounds and degradation of xenobiotics [50].

Thus, different mental disorders are characterized by differential gut microbial community which is generally predominated by a bacterial genus or a family. Notably, in some of the disorders, beneficial microbial population were overpopulated. For instance, abundance of *Lactobacillus* and *Bifidobacterium* in disorders like SCZ and ADHD, respectively. The probable reason for this can be attributed to the complexity of the gut microbiota. The adult microbiome generally shows the abundance of Firmicutes and Bacteroidetes phyla over other phyla with genera such as, *Clostridium* and *Bacteroides* as most prevalent [51]. In the

Indian gut, genus *Prevotella* is revealed to be predominant with core genera to include *Prevotella*, *Bacteroides*, *Roseburia* and *Megasphaera* [52]. Although due to variability in dietary habits, environment, health status, age, sex and season, it is impossible to set a criteria of ‘healthy’ or ‘normal’ gut microbiome but, an imbalance in gut microbiota of an individual should be considered characteristic of a disease. High abundance (more than the normal level) of beneficial genera, as found in certain mental disorders, in gut microbiome indicate imbalance and destabilized microbial community. Lower abundance of *Lactobacillus* and *Bifidobacterium* could be treated with a probiotic approach.

### Role and Scope of Psychobiotics

A very important therapeutic intervention for the treatment of mental disorders is the use of live microbes to restore the integrity of gut microbiota and to provide health benefits. The possibility of utilizing modern probiotics developed using latest advanced techniques has been shown to be very important and promising in the treatment of various diseases such as in obesity-related health complications [53, 54]. The term “psychobiotics” is defined as “a live organism that, when ingested in adequate amounts, produces a health benefit in patients suffering from psychiatric illness”. Since prebiotics (indigestible food material) also have a crucial role in the growth and activities of several beneficial bacteria in the gut, the prebiotics are also included in the definition of psychobiotics [55]. The effect of psychobiotics is very broad and have been demonstrated on regulation of neuroimmune axis, neural and hormonal pathways, inflammatory reflex, sympatho-adrenal medullary axis and in treating neuropsychiatric disorders [56, 57]. Table 2 lists psychobiotic strains which have shown potential in alleviating symptoms or in treatment of various mental disorders.

Psychobiotics have been tested and implicated as a part of treatment of various mental health disorders. For instance, the probiotic combination of *Lactobacillus helveticus* and *Bifidobacterium longum* fed to the volunteers daily for 30 days showed significant reduction in the psychological distress which was measured on clinical depression and anxiety scale [58]. Administration of another strain of *Bifidobacterium*, *B. longum* 1714 in healthy volunteers for four weeks resulted in reduction in stress and improvement in memory [59]. Another study demarcated the effect of *Bifidobacterium* and *Lactobacillus* strains in which probiotic food supplement intervention was made for 30 days with the multispecies probiotics containing *Bifidobacterium bifidum* W23, *Bifidobacterium lactis* W52, *Lactobacillus acidophilus* W37, *Lactobacillus brevis* W63, *Lactobacillus casei* W56,

*Lactobacillus salivarius* W24, and *Lactococcus lactis* (W19 and W58). Results showed a significantly reduced overall cognitive reactivity to sad mood, which was largely accounted for by reduced rumination and aggressive thoughts [60]. Probiotic milk containing strains of *Lactobacillus*, *L. acidophilus*, *L. casei*, *L. fermentum* and *Bifidobacterium bifidum* given for 12 weeks to AD patients resulted in decreased plasma and serum levels of malondialdehyde (MDA) and high-sensitivity C-reactive protein (hs-CRP), respectively. Other improvements included change in the  $\beta$ -cell function, insulin resistance and sensitivity in the patients indicating a positive effect on the cognitive function and some metabolic statuses in the AD patients [61]. Effect of probiotic supplements containing *Bifidobacterium bifidum* and *Lactobacillus* species including *L. acidophilus*, *L. reuteri* and *L. fermentum* was also observed in the Parkinson’s disease (PD) subjects for a period of twelve weeks. Movement Disorder Society-United Parkinson’s Rating Scales (MDS-UPDRS) scores were reduced in probiotic consumption group as compared to the placebo group [62]. In addition probiotic consumption also increased the insulin function in PD patients [62]. The intervention of *Lactobacillus plantarum* has shown to improve communication and behavior in ASD children [63]. Three probiotic strains *Lactobacillus acidophilus*, *L. rhamnosus* and *Bifidobacterium longum* were also used in a trial on ASD children in Egypt in which Autism and gastrointestinal (GI) distress symptoms were improved in the children after 12 weeks of treatment with the probiotic strains [64]. Moreover, after probiotic supplementation, the stool samples showed increases in *Bifidobacteria* and *Lactobacillus* colonies in autistic children [64]. Another probiotic strain, *Clostridium butyricum* has been shown to be markedly effective in alleviating cognitive dysfunction associated with vascular dementia in mice, possibly by acting through gut-microbiome-butyrate-brain axis [65]. It modulates CNS functions and reported to have impact on behavior and brain development [65].

Psychobiotics have opened a new and novel therapeutic approach to treat patients suffering from various psychiatric illnesses. Many probiotics, however, that have shown benefits in pre-clinical trials have not shown benefits in humans. For example, administration of *Lactobacillus rhamnosus* (JB-1) in healthy volunteers undergoing exam-related stress showed no effect on anxiety, mood, stress, or sleep [66]. Further, probiotics intervention studies in some disorders had been inconclusive, such as in BD [67]. Psychobiotics are under expensive exploration and more and more clinical trials are being conducted to demarcate the bacterial strains as potential candidates for treatment of mental disorders. Apart from the selection of a bacteria or group of bacteria, other parameters such as ensuring their prolonged stay in the body as many people expel probiotics from their body are also looked into [68]. Further, as

**Table 2** List of psychobiotic strains (as used in combinations or individually) and outcome of their use in treatment of mental disorders

Psychobiotic strains	Mental disorders	Outcome of their use	References
<i>Streptococcus vestibularis</i>	Schizophrenia	Improved social-behaviours	[38]
<i>Bifidobacterium longum</i>	Depression and anxiety	Reduction in the psychological distress	[58]
<i>Lactobacillus helveticus</i>			
<i>Bifidobacterium longum</i> 1714	Psychological distress	Reduction in stress and improvement in memory	[59]
<i>Bifidobacterium bifidum</i> W23	Mood disorders	Reduced rumination and aggressive thoughts	[60]
<i>Bifidobacterium lactis</i> W52			
<i>Lactobacillus acidophilus</i> W37			
<i>Lactobacillus brevis</i> W63			
<i>Lactobacillus casei</i> W56			
<i>Lactococcus lactis</i> W19			
<i>Lactococcus lactis</i> W58			
<i>Lactobacillus salivarius</i> W24			
<i>Bifidobacterium bifidum</i>	Alzheimer's disease	Revived cognitive and metabolic status	[61]
<i>Lactobacillus acidophilus</i>			
<i>Lactobacillus casei</i>			
<i>Lactobacillus fermentum</i>			
<i>Bifidobacterium bifidum</i>	Parkinson's disease	Downregulated cytokines and up regulated growth factor, peroxisome proliferator—activated receptor	[62]
<i>Lactobacillus acidophilus</i>			
<i>Lactobacillus fermentum</i>			
<i>Lactobacillus reuteri</i>			
<i>Lactobacillus plantarum</i>	ASD children	Improved communication and behaviour	[63]
<i>Bifidobacterium longum</i>	Autism spectrum disorder (ASD) in children	Improvement in autism and gastrointestinal (GI) symptoms	[64]
<i>Lactobacillus acidophilus</i>			
<i>Lactobacillus rhamnosus</i>			
<i>Clostridium butyricum</i>	Vascular dementia	Alleviating cognitive dysfunction by modulating CNS functions	[65]

individual's microbiota vary due to the specific physiology of the body, it is possible that the employment of psychobiotics and their effects may vary person to person.

Thus, several factors should be considered carefully for designing the appropriate therapeutic strategies for the treatment of mental disorders.

## Challenges and Future Directions

Mounting evidence over the past two decades have established the role of gut microbiome in various mental health disorders; however, before falling on the conclusive microbe-based therapeutic interventions, more robust data and clinical studies indicating the direct role of gut microbiota in restoring the mental health balance are required. There are numerous challenges that need to be addressed for better understanding of the causal or effector link between gut microbiota and wide range of mental health disorders. First, majority of the clinical studies conducted are cross-sectional and for better understanding of the impact of gut microbiota in mental health disorders or effect of any therapeutic intervention targeting gut microbiota, longitudinal studies are warranted [69]. Second, small sample size, lack of robustness and standardized sampling methodology and bioinformatics tools pose unique challenges and hamper the consistency and reproducibility of the results. Lack of comprehensive assessment of all symptoms, gender biasness and self-reporting of symptoms like in questionnaires on gastrointestinal problems, could give misleading interpretations. Though scientists have recognized these challenges and newer studies are better designed and conducted. Third, an important consideration, is that it has been extensively noted that diet plays an intricate role in the composition of an individual's gut microbiota and even short-term changes in the diet may result in significant alterations in the diversity and richness of gut microbiota [70]. Moreover, majority of mental health disorders are known to affect the appetite and metabolism of patients thereby adding another layer of complexity. Thus, monitoring the diet and lifestyle of both patients and healthy individuals under study, may present us with better understanding for designing the treatment plans. Furthermore, information regarding other interventions like medications and co-morbidities has been lacking in certain clinical studies and must be included. Lastly, it is speculated that every individual exhibits unique gut microbiome which depends on diet, genetics and lifestyle and could display differential responsiveness to treatment methods, such as; FMT, diet therapy, psychobiotics etc. posing another major challenge. Since 'microbiota-gut-brain' connection is a complex system encompassing many ways to modulate the gut microbiota and many mechanisms to affect the brain functioning, an integrative approach in which various therapeutic interventions can be employed in combinations for the treatment or mitigation of the disorder or its symptoms can be adopted. Since microbiota of individuals differ from each other and under different conditions, a personalized microbial-based therapy should be considered for effective treatment. Also,

studies focused on further understanding the biochemical basis of the microbiota-gut-brain interactions should be encouraged. Our understanding of the impact of gut microbiota in mental health conditions is limited by the use of rodent models and owing to the differences in humans, more clinical studies are warranted. In the coming times, advancements in new technologies and overcoming of the challenges discussed here, would allow thorough understanding of the extent gut microbiota controls the penetrance of mental health disorders and how it can be exploited for designing effective therapeutic interventions. Psychiatrists as well as microbiologists have been confronted with an important perspective of manifestation of mental health disorders; together they can work towards achieving or restoring the normal mental health balance in human population.

**Acknowledgements** HV and CDR acknowledge Ramjas College, University of Delhi, Delhi, India for providing infrastructural support. SP thank Department of Biotechnology (DBT), Government of India for Junior Research Fellowship in a project. PL thank University Grants Commission (UGC), Government of India for Senior Research Fellowship. SS and RL thank The Energy and Resources Institute (TERI), New Delhi, India for providing infrastructure facilities. RL acknowledges The National Academy of Sciences, India (NASI) for support under the NASI-Senior Scientist Platinum Jubilee Fellowship Scheme.

### Compliance with Ethical Standards

**Conflict of interest** The authors declare no competing interests.

## References

1. Cullen CM, Aneja KK, Beyhan S, Cho CE, Woloszynek S, Convertino M, McCoy SJ, Zhang Y, Anderson MZ, Alvarez-Ponce D, Smirnova E, Karstens L, Dorrestein PC, Li H, Sen Gupta A, Cheung K, Powers JG, Zhao Z, Rosen GL (2020) Emerging priorities for microbiome research. *Front Microbiol* 11:136. <https://doi.org/10.3389/fmicb.2020.00136>
2. Arnold WM, Hill ES, Fei N, Yee AL, Garcia MS, Cralle LE, Gilbert JA (2019) The human microbiome in health and disease. In: Netto G, Kaul K (eds) *Genomic applications in pathology*. Springer, Cham, pp 607–618. [https://doi.org/10.1007/978-3-319-96830-8\\_39](https://doi.org/10.1007/978-3-319-96830-8_39)
3. Singhvi N, Gupta V, Gaur M, Sharma V, Puri A, Singh Y, Dubey GP, Lal R (2020) Interplay of human gut microbiome in health and wellness. *Indian J Microbiol* 60:26–36. <https://doi.org/10.1007/s12088-019-00825-x>
4. Ekanayake A, Madegedara D, Chandrasekharan V, Magana-Arachchi D (2020) Respiratory bacterial microbiota and individual bacterial variability in lung cancer and bronchiectasis patients. *Indian J Microbiol* 60:196–205. <https://doi.org/10.1007/s12088-019-00850-w>
5. Rogers GB, Keating DJ, Young RL, Wong ML, Licinio J, Wesselingh S (2016) From gut dysbiosis to altered brain function and mental illness: mechanisms and pathways. *Mol Psychiatry* 21:738–748. <https://doi.org/10.1038/mp.2016.50>



6. Gupta V, Sood U, Kumar R, Lal R, Kalia VC (2020) Microbiome: a new lease to microbiology. *Indian J Microbiol* 60:1. <https://doi.org/10.1007/s12088-019-00852-8>
7. Sender R, Fuchs S, Milo R (2016) Revised estimates for the number of human and bacteria cells in the body. *PLoS Biol* 14:e1002533. <https://doi.org/10.1371/journal.pbio.1002533>
8. Kho ZY, Lal SK (2018) The human gut microbiome—a potential controller of wellness and disease. *Front Microbiol* 9:1835. <https://doi.org/10.3389/fmicb.2018.01835>
9. Dafale NA, Srivastava S, Purohit HJ (2020) Zoonosis: an emerging link to antibiotic resistance under “One Health Approach”. *Indian J Microbiol* 60:139–152. <https://doi.org/10.1007/s12088-020-00860-z>
10. Carabotti M, Scirocco A, Maselli MA, Severi C (2015) The gut-brain axis: interactions between enteric microbiota, central and enteric nervous systems. *Ann Gastroenterol* 28:203–209
11. Dinan TG, Cryan JF (2017) The microbiome-gut-brain axis in health and disease. *Gastroenterol Clin North Am* 46:77–89. <https://doi.org/10.1016/j.gtc.2016.09.007>
12. GBD (2017) Disease and Injury Incidence and Prevalence Collaborators (2018) Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease study 2017. *Lancet* 392:1789–1858. [https://doi.org/10.1016/S0140-6736\(18\)32279-7](https://doi.org/10.1016/S0140-6736(18)32279-7)
13. Bastiaanssen TFS, Cusotto S, Claesson MJ, Clarke G, Dinan TG, Cryan JF (2020) Gutted! unraveling the role of the microbiome in major depressive disorder. *Harv Rev Psychiatry* 28:26–39. <https://doi.org/10.1097/HRP.0000000000000243>
14. Caspani G, Kennedy S, Foster JA, Swann J (2019) Gut microbial metabolites in depression: understanding the biochemical mechanisms. *Microb Cell* 6:454–481. <https://doi.org/10.15698/mic2019.10.693>
15. Neufeld KM, Kang N, Bienenstock J, Foster JA (2011) Reduced anxiety-like behavior and central neurochemical change in germ-free mice. *Neurogastroenterol Motil* 23(255–264):e119. <https://doi.org/10.1111/j.1365-2982.2010.01620.x>
16. Bravo JA, Forsythe P, Chew MV, Escaravage E, Savignac HM, Dinan TG, Bienenstock J, Cryan JF (2011) Ingestion of *Lactobacillus* strain regulates emotional behavior and central GABA receptor expression in a mouse via the vagus nerve. *Proc Natl Acad Sci USA* 108:16050–16055. <https://doi.org/10.1073/pnas.1102999108>
17. Roubalova R, Prochazkova P, Papezova H, Smitka K, Bilej M, Taskalova-Hogenova H (2020) Anorexia nervosa: gut microbiota-immune-brain interactions. *Clin Nutr* 39:676–684. <https://doi.org/10.1016/j.clnu.2019.03.023>
18. Unger MM, Spiegel J, Dillmann KU, Grundmann D, Philippeit H, Burmann J, Fassbender K, Schwierz A, Schafer KH (2016) Short chain fatty acids and gut microbiota differ between patients with Parkinson’s disease and age-matched controls. *Parkinsonism Relat Disord* 32:66–72. <https://doi.org/10.1016/j.parkreldis.2016.08.019>
19. Zhang L, Wang Y, Xiayu X, Shi C, Chen W, Song N, Fu X, Zhou R, Xu YF, Huang L, Zhu H, Han Y, Qin C (2017) Altered gut microbiota in a mouse model of Alzheimer’s disease. *J Alzheimers Dis* 60:1241–1257. <https://doi.org/10.3233/JAD-170020>
20. Wang L, Christophersen CT, Sorich MJ, Gerber JP, Angley MT, Conlon MA (2012) Elevated fecal short chain fatty acid and ammonia concentrations in children with autism spectrum disorder. *Dig Dis Sci* 57:2096–2102. <https://doi.org/10.1007/s10620-012-2167-7>
21. Galland L (2014) The gut microbiome and the brain. *J Med Food* 17:1261–1272. <https://doi.org/10.1089/jmf.2014.7000>
22. Golubeva AV, Joyce SA, Moloney G, Burokas A, Sherwin E, Arbolea S, Flynn I, Khochanskiy D, Moya-Perez A, Peterson V, Rea K, Murphy K, Makarova O, Buravkov S, Hyland NP, Stanton C, Clarke G, Gahan CGM, Dinan TG, Cryan JF (2017) Microbiota-related changes in bile acid & tryptophan metabolism are associated with gastrointestinal dysfunction in a mouse model of autism. *EBioMedicine* 24:166–178. <https://doi.org/10.1016/j.ebiom.2017.09.020>
23. Kim YK, Shin C (2018) The microbiota-gut-brain axis in neuropsychiatric disorders: pathophysiological mechanisms and novel treatments. *Curr Neuropharmacol* 16:559–573. <https://doi.org/10.2174/1570159X15666170915141036>
24. Sagar R, Dandona R, Gururaj G, Dhaliwal RS, Singh A, Ferrari A, Dua T, Ganguli A, Varghese M, Chakma JK, Kumar GA, Shaji KS, Ambekar A, Rangaswamy T, Vijayakumar L, Agarwal V, Krishnankutty RP, Bhatia R, Charlson F, Chowdhary N, Erskine HE, Glenn SD, Krish V, Mantilla Herrera AM, Mutreja P, Odell CM, Pal PK, Prakash S, Santomauro D, Shukla DK, Singh R, Singh RKL, Thakur JS, ThekkePurakkal AS, Varghese CM, Reddy KS, Swaminathan S, Whiteford H, Bekedam HJ, Murray CJL, Vos T, Dandona L (2020) The burden of mental disorders across the states of India: the global burden of disease study 1990–2017. *Lancet Psychiatry* 7:148–161. [https://doi.org/10.1016/S2215-0366\(19\)30475-4](https://doi.org/10.1016/S2215-0366(19)30475-4)
25. Bundgaard-Nielsen C, Knudsen J, Leutscher PDC, Lauritsen MB, Nyegaard M, Hagström S, Sørensen S (2020) Gut microbiota profiles of autism spectrum disorder and attention deficit/hyperactivity disorder: a systematic literature review. *Gut Microbes*. <https://doi.org/10.1080/19490976.2020.1748258>
26. Kang D, Adams JB, Coleman D, Pollard EL, Maldonado J, McDonough-Means S, Caporaso JG, Krajmalnik-Brown S (2019) Long-term benefit of Microbiota Transfer Therapy on autism symptoms and gut microbiota. *Sci Rep* 9:5821. <https://doi.org/10.1038/s41598-019-42183-0>
27. Prehn-Kristensen A, Zimmermann A, Tittmann L, Lieb W, Schreiber S, Baving L, Fischer A (2018) Reduced microbiome alpha diversity in young patients with ADHD. *PLoS ONE* 13:e0200728. <https://doi.org/10.1371/journal.pone.0200728>
28. Woo HD, Kim DW, Hong YS, Kim YM, Seo JH, Choe BM, Park JH, Kang JW, Yoo JH, Chueh HW, Lee JH, Kwak MJ, Kim J (2014) Dietary patterns in children with attention deficit/hyperactivity disorder (ADHD). *Nutrients* 6:1539–1553. <https://doi.org/10.3390/nu6041539>
29. Jiang HY, Zhang X, Yu ZH, Zhang Z, Deng M, Zhao JH, Ruan B (2018) Altered gut microbiota profile in patients with generalized anxiety disorder. *J Psychiatr Res* 104:130–136. <https://doi.org/10.1016/j.jpsychires.2018.07.007>
30. Yang B, Wei J, Ju P, Chen J (2019) Effects of regulating intestinal microbiota on anxiety symptoms: a systematic review. *Gen Psychiatr* 32:e100056. <https://doi.org/10.1136/gpsych-2019-100056>
31. Valles-Colomer M, Falony G, Darzi Y, Tigchelaar EF, Wang J, Tito RY, Schiweck C, Kurilshikov A, Joossens M, Wijnemga C, Claes S, Van Oudenhove L, Zhernakova A, Vieira-Silva S, Valles-Colomer M, Falony G, Darzi Y, Tigchelaar EF, Wang J, Tito RY, Schiweck C, Kurilshikov A, Joossens M, Wijnemga C, Claes S, Van Oudenhove L, Zhernakova A, Vieira-Silva S, Raes J (2019) The neuroactive potential of the human gut microbiota in quality of life and depression. *Nat Microbiol* 4:623–632. <https://doi.org/10.1038/s41564-018-0337-x>
32. Huang TT, Lai JB, Du YL, Xu Y, Ruan LM, Hu SH (2019) Current understanding of gut microbiota in mood disorders: an update of human studies. *Front Genet* 10:98. <https://doi.org/10.3389/fgene.2019.00098>
33. Hu S, Li A, Huang T, Lai J, Li J, Sublette ME, Lu H, Lu Q, Du Y, Hu Z, Ng CH, Zhang H, Lu J, Mou T, Lu S, Wang D, Duan J, Hu



- J, Huang M, Wei N, Zhou W, Ruan L, Li MD, Xu Y (2019) Gut microbiota changes in patients with bipolar depression. *Adv Sci (Weinh)* 6:1900752. <https://doi.org/10.1002/adv.201900752>
34. Rucklidge JJ, Harrison R (2010) Successful treatment of bipolar disorder II and ADHD with a micronutrient formula: a case study. *CNS Spectr* 15:289–295. <https://doi.org/10.1017/s1092852900027516>
  35. Flowers SA, Ward KM, Clark CT (2020) The gut microbiome in bipolar disorder and pharmacotherapy management. *Neuropsychobiology* 79:43–49. <https://doi.org/10.1159/000504496>
  36. Fond GB, Lagier JC, Honore S, Lancon C, Korchia T, Sunhary De Verville PL, Llorca PM, Auquier P, Guedj E, Boyer L (2020) Microbiota-orientated treatments for major depression and schizophrenia. *Nutrients* 12:1024. <https://doi.org/10.3390/nu12041024>
  37. Szeligowski T, Yun AL, Lennox BR, Burnet PWJ (2020) The gut microbiome and schizophrenia: the current state of the field and clinical applications. *Front Psychiatry* 11:156. <https://doi.org/10.3389/fpsy.2020.00156>
  38. Zhu F, Ju Y, Wang W, Wang Q, Guo R, Ma Q, Sun Q, Fan Y, Xie Y, Yang Z, Jie Z, Zhao B, Xiao L, Yang L, Zhang T, Feng J, Guo L, He X, Chen Y, Chen C, Gao C, Xu X, Yang H, Wang J, Dang Y, Madsen L, Brix S, Kristiansen K, Jia H, Ma X (2020) Metagenome-wide association of gut microbiome features for schizophrenia. *Nat Commun* 11:1612. <https://doi.org/10.1038/s41467-020-15457-9>
  39. Seitz J, Belheouane M, Schulz N, Dempfle A, Baines JF, Herpertz-Dahlmann B (2019) The impact of starvation on the microbiome and gut-brain interaction in anorexia nervosa. *Front Endocrinol (Lausanne)* 10:41. <https://doi.org/10.3389/fendo.2019.00041>
  40. Hata T, Miyata N, Takakura S, Yoshihara K, Asano Y, Kimura-Todani T, Yamashita M, Zhang XT, Watanabe N, Mikami K, Koga Y, Sudo N (2019) The gut microbiome derived from anorexia nervosa patients impairs weight gain and behavioral performance in female mice. *Endocrinology* 160:2441–2452. <https://doi.org/10.1210/en.2019-00408>
  41. Leclercq S, Starkel P, Delzenne NM, de Timary P (2019) The gut microbiota: a new target in the management of alcohol dependence? *Alcohol* 74:105–111. <https://doi.org/10.1016/j.alcohol.2018.03.005>
  42. Meckel KR, Kiraly DD (2019) A potential role for the gut microbiome in substance use disorders. *Psychopharmacology* 236:1513–1530. <https://doi.org/10.1007/s00213-019-05232-0>
  43. Bajaj JS, Sikaroodi M, Fagan A, Heuman D, Gilles H, Gavis EA, Fuchs M, Gonzalez-Maeso J, Nizam S, Gillevet PM, Wade JB (2019) Posttraumatic stress disorder is associated with altered gut microbiota that modulates cognitive performance in veterans with cirrhosis. *Am J Physiol Gastrointest Liver Physiol* 317:G661–G669. <https://doi.org/10.1152/ajpgi.00194.2019>
  44. Xu M, Wang C, Krolick KN, Shi H, Zhu J (2020) Difference in post-stress recovery of the gut microbiome and its altered metabolism after chronic adolescent stress in rats. *Sci Rep* 10:3950. <https://doi.org/10.1038/s41598-020-60862-1>
  45. Li Y, Hao Y, Fan F, Zhang B (2018) The role of microbiome in insomnia, circadian disturbance and depression. *Front Psychiatry* 9:669. <https://doi.org/10.3389/fpsy.2018.00669>
  46. Zhang J, Bi JJ, Guo GJ, Yang L, Zhu B, Zhan GF, Li S, Huang NN, Hashimoto K, Yang C, Luo AL (2019) Abnormal composition of gut microbiota contributes to delirium-like behaviors after abdominal surgery in mice. *CNS Neurosci Ther* 25:685–696. <https://doi.org/10.1111/cns.13103>
  47. Saji N, Niida S, Murotani K, Hisada T, Tsuduki T, Sugimoto T, Kimura A, Toba K, Sakurai T (2019) Analysis of the relationship between the gut microbiome and dementia: a cross-sectional study conducted in Japan. *Sci Rep* 9:1008. <https://doi.org/10.1038/s41598-018-38218-7>
  48. Angelucci F, Cechova K, Amlerova J, Hort J (2019) Antibiotics, gut microbiota, and Alzheimer's disease. *J Neuroinflammation* 16:108. <https://doi.org/10.1186/s12974-019-1494-4>
  49. Adler CH, Beach TG (2016) Neuropathological basis of non-motor manifestations of Parkinson's disease. *Mov Disord* 31:1114–1119. <https://doi.org/10.1002/mds.26605>
  50. Hill-Burns EM, Debelius JW, Morton JT, Wissemann WT, Lewis MR, Wallen ZD, Peddada SD, Factor SA, Molho E, Zabetian CP, Knight R, Payami H (2017) Parkinson's disease and Parkinson's disease medications have distinct signatures of the gut microbiome. *Mov Disord* 32:739–749. <https://doi.org/10.1002/mds.26942>
  51. Rinninella E, Raoul P, Cintoni M, Franceschi F, Miggianno GAD, Gasbarrini A, Mele MC (2019) What is the healthy gut microbiota composition? A changing ecosystem across age, environment, diet, and diseases. *Microorganisms* 7:14. <https://doi.org/10.3390/microorganisms7010014>
  52. Kulkarni AS, Kumbhare SV, Dhotre DP, Shouche YS (2019) Mining the core gut microbiome from a sample Indian population. *Indian J Microbiol* 59:90–95. <https://doi.org/10.1007/s12088-018-0742-0>
  53. Kumar R, Sood U, Gupta V, Singh M, Scaria J, Lal R (2020) Recent advancements in the development of modern probiotics for restoring human gut microbiome dysbiosis. *Indian J Microbiol* 60:12–25. <https://doi.org/10.1007/s12088-019-00808-y>
  54. Naumova N, Alikina T, Tupikin A, Kalmykova A, Soldatova G, Vlassov V, Kabilov M (2020) Human gut microbiome response to short-term *Bifidobacterium*-based probiotic treatment. *Indian J Microbiol*. <https://doi.org/10.1007/s12088-020-00888-1>
  55. Sarkar A, Lehto SM, Harty S, Dinan TG, Cryan JF, Burnet PWJ (2016) Psychobiotics and the manipulation of bacteria-gut-brain signals. *Trends Neurosci* 39:763–781. <https://doi.org/10.1016/j.tins.2016.09.002>
  56. Barbosa RSD, Vieira-Coelho MA (2020) Probiotics and prebiotics: focus on psychiatric disorders—a systematic review. *Nutr Rev* 78:437–450. <https://doi.org/10.1093/nutrit/nuz080>
  57. Ansari F, Pourjafar H, Tabrizi A, Homayouni A (2020) The effects of probiotics and prebiotics on mental disorders: a review on depression, anxiety, alzheimer, and autism spectrum disorders. *Curr Pharm Biotechnol* 21:555–565. <https://doi.org/10.2174/138920121666200107113812>
  58. Messaoudi M, Lalonde R, Violle N, Javelot H, Desor D, Nejdi A, Bisson JF, Rougeot C, Pichelin M, Cazaubiel M, Cazaubiel JM (2011) Assessment of psychotropic-like properties of a probiotic formulation (*Lactobacillus helveticus* R0052 and *Bifidobacterium longum* R0175) in rats and human subjects. *Br J Nutr* 105:755–764. <https://doi.org/10.1017/S0007114510004319>
  59. Allen AP, Hutch W, Borre YE, Kennedy PJ, Temko A, Boylan G, Murphy E, Cryan JF, Dinan TG, Clarke G (2016) *Bifidobacterium longum* 1714 as a translational psychobiotic: modulation of stress, electrophysiology and neurocognition in healthy volunteers. *Transl Psychiatry* 6:e939. <https://doi.org/10.1038/tp.2016.191>
  60. Steenbergen L, Sellaro R, van Hemert S, Bosch JA, Colzato LS (2015) A randomized controlled trial to test the effect of multi-species probiotics on cognitive reactivity to sad mood. *Brain Behav Immun* 48:258–264. <https://doi.org/10.1016/j.bbi.2015.04.003>
  61. Akbari E, Asemi Z, Daneshvar Kakhaki R, Bahmani F, Kouchaki E, Tamtaji OR, Hamidi GA, Salami M (2016) Effect of probiotic supplementation on cognitive function and metabolic status in Alzheimer's disease: a randomized, double-blind and controlled trial. *Front Aging Neurosci* 8:256. <https://doi.org/10.3389/fnagi.2016.00256>

62. Tamtaji OR, Taghizadeh M, Daneshvar Kakhaki R, Kouchaki E, Bahmani F, Borzabadi S, Oryan S, Mafi A, Asemi Z (2019) Clinical and metabolic response to probiotic administration in people with Parkinson's disease: a randomized, double-blind, placebo-controlled trial. *Clin Nutr* 38:1031–1035. <https://doi.org/10.1016/j.clnu.2018.05.018>
63. Nimgampalle M, Kuna Y (2017) Anti-Alzheimer properties of probiotic, *Lactobacillus plantarum* MTCC 1325 in Alzheimer's disease induced albino rats. *J Clin Diagn Res* 11:KC01–KC05. <https://doi.org/10.7860/JCDR/2017/26106.10428>
64. Shaaban SY, El Gendy YG, Mehanna NS, El-Senousy WM, El-Feki HSA, Saad K, El-Asheer OM (2018) The role of probiotics in children with autism spectrum disorder: a prospective, open-label study. *Nutr Neurosci* 21:676–681. <https://doi.org/10.1080/1028415X.2017.1347746>
65. Liu J, Sun J, Wang F, Yu X, Ling Z, Li H, Zhang H, Jin J, Chen W, Pang M, Yu J, He Y, Xu J (2015) Neuroprotective effects of *Clostridium butyricum* against vascular dementia in mice via metabolic butyrate. *Biomed Res Int* 2015:412946. <https://doi.org/10.1155/2015/412946>
66. Kelly JR, Allen AP, Temko A, Hutch W, Kennedy PJ, Farid N, Murphy E, Boylan G, Bienenstock J, Cryan JF, Clarke G, Dinan TG (2017) Lost in translation? The potential psychobiotic *Lactobacillus rhamnosus* (JB-1) fails to modulate stress or cognitive performance in healthy male subjects. *Brain Behav Immun* 61:50–59. <https://doi.org/10.1016/j.bbi.2016.11.018>
67. Reininghaus EZ, Wetzlmair LC, Fellendorf FT, Platzer M, Queissner R, Birner A, Pilz R, Hamm C, Maget A, Koidl C, Riedrich K, Klampfer K, Ferk K, Dalkner N (2020) The impact of probiotic supplements on cognitive parameters in euthymic individuals with bipolar disorder: a pilot study. *Neuropsychobiology* 79:63–70. <https://doi.org/10.1159/000492537>
68. Zmora N, Zilberman-Schapira G, Suez J, Mor U, Dori-Bachash M, Bashiardes S, Kotler E, Zur M, Regev-Lehavi D, Brik RB, Federici S, Cohen Y, Linevsky R, Rothschild D, Moor AE, Ben-Moshe S, Harmelin A, Itzkovitz S, Maharshak N, Shibolet O, Shapiro H, Pevsner-Fischer M, Sharon I, Halpern Z, Segal E, Elinav E (2018) Personalized gut mucosal colonization resistance to empiric probiotics is associated with unique host and microbiome features. *Cell* 174:1388–1405.e21. <https://doi.org/10.1016/j.cell.2018.08.041>
69. Järbrink-Sehgal E, Andreasson A (2020) The gut microbiota and mental health in adults. *Curr Opin Neurobiol* 62:102–114. <https://doi.org/10.1016/j.conb.2020.01.016>
70. Godos J, Currenti W, Angelino D, Mena P, Castellano S, Caraci F, Galvano F, Del Rio D, Ferri R, Grosso G (2020) Diet and mental health: review of the recent updates on molecular mechanisms. *Antioxidants (Basel)* 9:346. <https://doi.org/10.3390/antiox9040346>

**Publisher's Note** Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.