Brain–gut–microbiota axis in depression: A historical overview and future directions

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ABSTRACT

Depression is the most common mental disorder and a leading cause of disability worldwide. Despite abundant research, the precise mechanisms underlying the pathophysiology of depression remain elusive. Accumulating evidence from preclinical and clinical studies suggests that alterations in the gut microbiota, microbe-derived short-chain fatty acids, D-amino acids and metabolites play a key role in the pathophysiology of depression via the brain–gut–microbiota axis, including the neural and immune systems. Notably, the brain–gut–microbiota axis might play a crucial role in susceptibility versus resilience in rodents exposed to stress. Vagotomy is reported to block depression-like phenotypes in rodents after fecal microbiota transplantation of "depression-related" microbiome, suggesting that the vagus nerve influences depression through the brain–gut–microbiota axis. In this article, we review recent findings regarding the brain–gut–microbiota axis in depression and discuss its potential as a therapeutic target for depression.

1. Introduction

Depression has received substantial attention from researchers and the general public, particularly due to its link to suicide. It is estimated that 280 million people of all ages, and 5.0% of adults, are affected by depression worldwide (Global Health Data Exchange, 2021). This high global burden of disease dramatically affects individuals' and families' abilities to live a rewarding life (GBD, 2019 Disease and Injuries Collaborators, 2020; Friedrich, 2017; Global Health Data Exchange, 2021). In 2020, 5683 unique data sources from the global burden of disease study showed that the prevalence of depression or anxiety disorders has significantly increased due to the COVID-19 pandemic (COVID-19 Mental Disorders Collaborators, 2021). At present, the available treatments operate on the main principle of abnormal brain chemistry in depression. Due to treatment resistant depression and the delayed onset of first-line antidepressants, such as selective serotonin reuptake

inhibitors (SSRIs) and serotonin–norepinephrine reuptake inhibitors (SNRIs), the needs of many depression patients are unmet, even with complementary therapies such as inter-personal psychotherapy and non-pharmacological therapy such as electroconvulsive therapy (Beurel et al., 2020; Wei et al., 2021). One challenge is that the precise mechanisms underlying the pathophysiology of depression remain unknown. Unlocking the biological mechanisms of depression is still a work in progress. A new perspective targeting the brain–gut–microbiota axis might more closely resemble the ground truth in depression, and could thus contribute to the development of new antidepressant drugs.

Over the last decade, accumulating evidence suggests that the brain–gut–microbiota axis is responsible for the pathophysiology of depression (Foster and McVey Neufeld, 2013; Simpson et al., 2021; Valles-Colomer et al., 2019). Causality studies have suggested that the depression phenotype is accompanied by alterations in the gut microbiota which, in turn, affect depression-like behaviors and increase the

risk of depression (Foster and McVey Neufeld, 2013; Lach et al., 2018; Martin et al., 2018; Vuong et al., 2017; Yang et al., 2020b). Patients with depression experience the feeling of anhedonia in daily activities and report systemic behavioral symptoms like loss of energy or increased fatigue. Furthermore, alterations in the gut microbiota and its related metabolic disturbance have been increasingly characterized in patients with depression (Jiang et al., 2015; Naseribafrouei et al., 2014; Yang et al., 2020a; Zheng et al., 2020b, 2016). Various animal models of depression have shown that abnormal composition of the gut microbiota is associated with depression-like behaviors (Dinan and Cryan, 2013; Park et al., 2013; Tillmann et al., 2019; Vuong et al., 2017; Yang et al., 2020b).

In this article, we review the role of the brain–gut–microbiota axis in depression. This article provides a summary of the scientific basis that the brain–gut–microbiota axis influences mental health disorders, including depression (Lach et al., 2018; Martin et al., 2018). We then discuss the bidirectional and mutually interacting network targeting the brain–gut–microbiota axis in depression.

2. The brain–gut–microbiota system

In 1980, the concept of a gut–brain axis was unexpectedly born due to research findings on hormone signaling of the gastrointestinal endocrine system in neurons and brain cells (Track, 1980). In the following decades, the concept has been further strengthened and expanded to include the microbiome's contribution to the gut–brain axis (Carabotti et al., 2015; Hsiao et al., 2013; Margolis et al., 2021). At present, the brain–gut–microbiota denotes more than just the concept of the brain–gut–microbiota axis, it also represents the brain–gut–microbiota system in hosts and interactions among central nervous system (CNS), endocrine chemical signal system, immune regulation, microbiota and metabolic effects, and barrier functions in the brain and gut (Fig. 1). The coordination of these factors plays an important role in maintaining an individual's state of health (Foster and McVey Neufeld, 2013; Lynch and Pedersen, 2016; Maiuolo et al., 2021; Margolis et al., 2021). If imbalance exists in the brain–gut–microbiota axis, various kinds of diseases—including mental health disorders like depression—may occur (Foster and McVey Neufeld, 2013; Lynch and Pedersen, 2016; Maiuolo et al., 2021; Margolis et al., 2021).

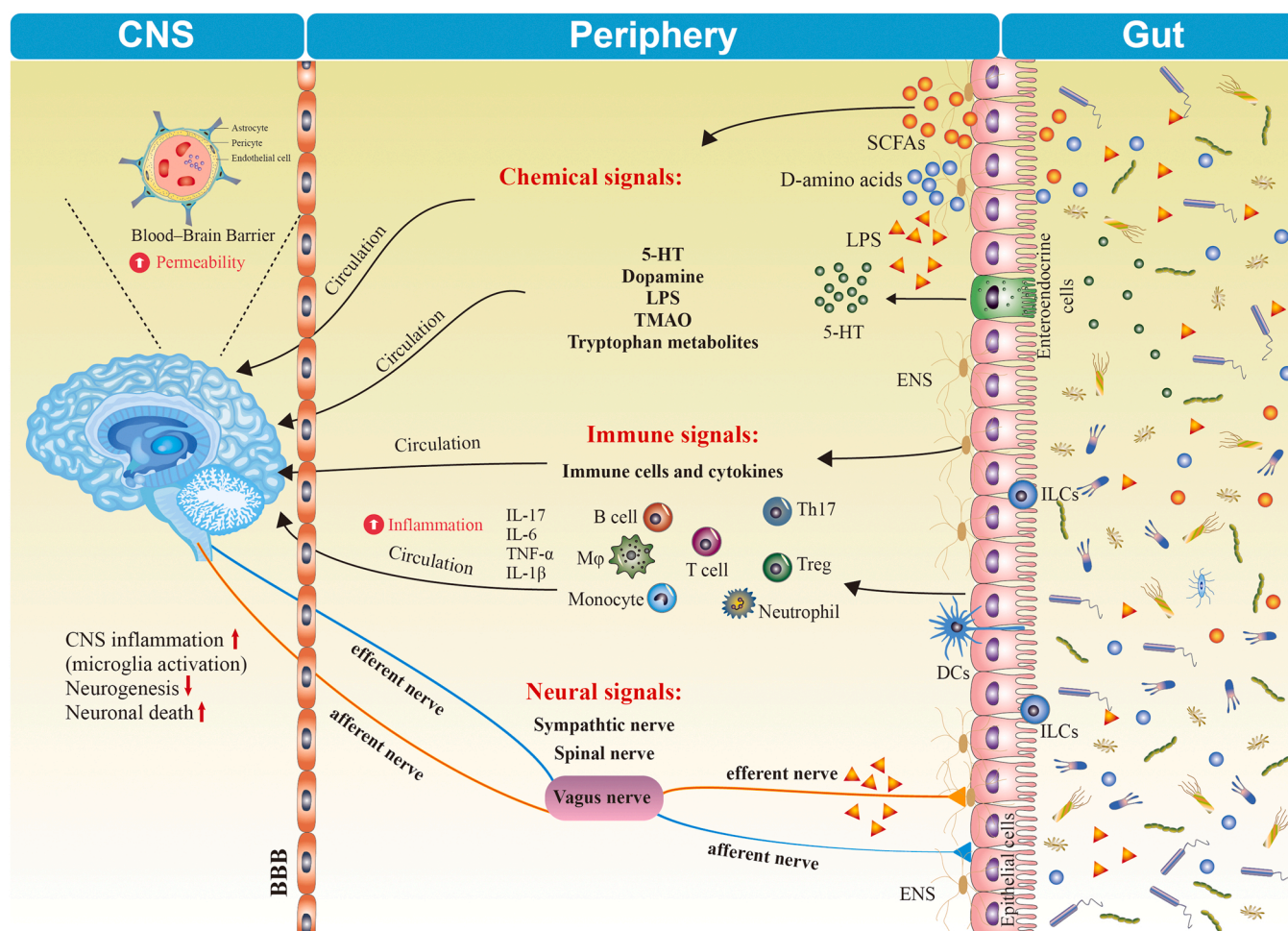The microbiome is mainly made up of bacteria, viruses, archaea, and

Fig. 1. The role of the brain–gut–microbiota axis in the body. The major pathways of the brain–gut–microbiota axis are shown among the central nervous system (CNS), periphery, and gut. The network of neural signals, immune signals, and chemical signals constitutes a major part of the brain–gut–microbiota axis. Alterations in this network involves complex interactions across organs by direct (nerves) and indirect (systemic circulation) pathways, contributing to altered homeostasis in the body. Changes in the gut microbiota composition and microbiome-derived SCFAs, D-amino acids and metabolites can alter neural signals, immune signals, and chemical signals to cause depression. The CNS works through neural regulation, neurotransmitters, immune signals, and other factors that target peripheral organs and tissue in response to different signal reflexes, thereby contributing to normal bidirectional brain–gut axis signaling. When this balance is destroyed by stress, depression or other diseases may occur. CNS: central nervous system, 5-HT: 5-hydroxytryptamine, IL-6: interleukin 6, IL-17: interleukin 17, IL-1β: interleukin 1β, ILC: innate lymphoid cells, LPS: lipopolysaccharide, SCFA: short chain fatty acid, TMAO: trimethylamine *N*-oxide, TNF-α: tumor necrosis factor α. Some materials of the figure have been designed by using the resources from Freepik.com.

fungi at the order of magnitude of a trillion microbes; as a result, the ratio is nearly 1:1 of bacterial to human cells in the body, although the genomic content of the microbiome contains more than 100-fold more genes than the human genome (Douglas et al., 2020; Lynch and Pedersen, 2016; Sender et al., 2016; Thursby and Juge, 2017; Zhu et al., 2010). The gut microbiota plays essential roles involving digestion and absorption from the diet, defending the gastrointestinal tract from pathogens, and secreting essential vitamins such as folic acid and vitamin K for overall bodily health (O'Hara and Shanahan, 2006; Rowland et al., 2018). In recent years, more and more studies have found that the gut microbiota and host have a mutually beneficial relationship starting from the earliest stages of embryonic life by way of the mother–to–child connection, affecting infant brain development and mental health (Codagnone et al., 2019; Milani et al., 2017). Studies have demonstrated that the gut microbiota interacts with the CNS through multiple routes, further deepening our understanding of its influence on mental health, including depression (Foster and McVey Neufeld, 2013; Morais et al., 2021; Simpson et al., 2021).

Neural signal networks in the brain–gut–microbiota system are important and fast response routes, including the enteric nervous system (ENS), vagus nerves and spinal nerves. The ENS, which is also known as the "brain in the gut" or "second brain," controls the gut's external and internal environment (Ganz, 2021; Margolis et al., 2021; Niesler et al., 2021). The complex regulation of the ENS serves a multifaceted role in modulating microbial composition, microbiota-related metabolites, neurotransmitter and immune signaling, and protection of the intestinal barrier (Margolis et al., 2021; Yoo and Mazmanian, 2017). Thus, bidirectional communication between the CNS and ENS, as well as other signals, forms part of the network for the brain–gut–microbiota axis. The vagal pathway has been repeatedly identified as the most direct link for microflora signals to reach the brain (Morais et al., 2021). On one hand, the vagus nerve is responsible for regulating metabolic homeostasis and feeding behavior, such as gastrointestinal motility and secretion functions (Pavlov and Tracey, 2012). On the other hand, the vagus nerve is involved in the mechanism of the inflammatory actions among the brain, gut, and other organs in the body (Pavlov and Tracey, 2012). Through its afferent and efferent arms, the vagus nerve senses inflammatory cytokines mediated by pattern recognition receptors (PRRs), such as toll-like receptors (TLRs), and then integrates afferent signaling into the brain; it also plays an output function in regulating immune activation and inhibiting pro-inflammatory cytokine release from the gut or other organs by the efferent arm, thereby contributing to the inflammatory reflex (Pavlov and Tracey, 2012). In addition, acetylcholine receptors/ligands mediating the cholinergic anti-inflammatory pathway via the vagus nerve have also been proposed as an important immune modulator in the gut microbiota that communicates with the brain (Bonaz et al., 2018; Pavlov and Tracey, 2012).

The immune signal network in the brain–gut–microbiota system is a complicated bidirectional signaling route with functions that extend beyond neuroinflammation. Activation of the immune system induced by the gut microbiota occurs not only in the intestinal immune system but also through long-distance regulation of brain immune cells (Fung et al., 2017; Salvo-Romero et al., 2020). Both innate and adaptive immune responses have been associated with the gut microbiota and brain. The innate immune system related to the brain–gut–microbiota axis mainly includes monocytes and macrophages in the peripheral system, glial cells like microglia and astrocyte in the brain, and dendritic cells (DCs) and innate lymphoid cells in the gut (Salvo-Romero et al., 2020; Zheng et al., 2020a). For example, monocytes and dendritic cells can establish interaction signals in the brain–gut–microbiota axis through PRRs that are indirectly activated or directly mediated by gut microbiota or microbiota-related products (Salvo-Romero et al., 2020; Sun et al., 2020a; Zheng et al., 2020a). In the adaptive immune system, Th17 and Treg cells are important immune effectors in the brain–gut–microbiota axis related to microbiome-immunity crosstalk in homeostasis and disease (Salvo-Romero et al., 2020; Zheng et al., 2020a). In addition, the

gut barrier and blood–brain barrier (BBB) protect against invasion by external pathogenic microbes or related abnormal signal molecules, which all must be balanced by the innate and adaptive immune system (Margolis et al., 2021).

Research on chemical signal networks has advanced our understanding of the specific role of the brain–gut–microbiota system. Certain gut microorganisms can synthesize or produce gut-related metabolites, neuroactive modulators, and other molecules through bacterial breakdown or intestinal cell secretion (Averina et al., 2020; Parker et al., 2020). Short-chain fatty acids (SCFAs) are the main kind of metabolite in the gut that targets immune cells, neurons, endocrine cells, and intestinal epithelial cells (Averina et al., 2020; Dalile et al., 2019; Silva et al., 2020). SCFAs with a length of 2–6 carbons mainly comprise acetate, propionate, and butyrate, and occasionally formic acid, iso-butyric acid, valeric acid, isovaleric acid, and caproic acid (Lourenco et al., 2019). These SCFAs modulating gut and brain functional interactions may be involved in multiple routes, such as neural signals (vagus nerve), immune signals (Th17, Treg, microglia), and chemical signals [brain-derived neurotrophic factor (BDNF), glia-derived neurotrophic factor (GDNF)] (Dalile et al., 2019; Silva et al., 2020). Neuroactive modulators, including serotonin (5-hydroxytryptamine: 5-HT), γ-aminobutyric acid (GABA), and BDNF, are also interactively regulated by the gut–brain axis (Morais et al., 2021). Various other chemical signaling molecules, such as tryptophan metabolites, trimethylamine-N-oxide (TMAO), and lipopolysaccharide (LPS), are also involved in the brain–gut–microbiota axis and can contribute to health and disease (Caspani et al., 2019; Kiecolt-Glaser et al., 2018; Parker et al., 2020; Zheng et al., 2013). Thus, chemical signals produced by specific gut microbiota seem to have specific roles in various biological processes in relation to the brain–gut–microbiota axis for health and disease.

3. Role of the brain–gut–microbiota in depression

3.1. Findings from rodent models

It is well recognized that stress plays a role in the pathophysiology of depression and that resilience is mediated by adaptive changes in several circuits, including BDNF, pro-inflammatory cytokines, and spleen (Hashimoto, 2019, 2020; Qu et al., 2017; Yang et al., 2015a, 2015b, 2016a; Zhang et al., 2021). Studies have shown that some rodents are resilient to chronic social defeat stress (CSDS) and learned helplessness (LH). Our group reported higher levels of *Bifidobacterium* in CSDS resilient mice compared with control and CSDS susceptible mice (Yang et al., 2017a). Furthermore, oral administration of *Bifidobacterium* significantly increased the number of mice resilient to CSDS compared with vehicle treatment (Yang et al., 2017a), suggesting that *Bifidobacterium* confers resilience to CSDS. We also reported that the relative abundances of the genera *Lactobacillus*, *Clostridium cluster III*, and *Anaerofustis* in LH susceptible rats were significantly higher than those in control and LH resilient rats, and that the levels of acetic acid and propionic acid in the feces of LH susceptible rats were lower than those in control and LH resilient rats (Zhang et al., 2019a). Interestingly, antibiotic-induced microbiome depletion is associated with resilience to CSDS in mice (Wang et al., 2020c). It has also been reported that betaine supplementation contributes to resilience to anhedonia in mice subjected to CSDS through anti-inflammatory actions (Qu et al., 2020). Taken together, these findings support that the brain–gut–microbiota axis plays a role in susceptibility and resilience to stress (Hashimoto, 2020; Wei et al., 2021).

Increasing evidence from preclinical studies suggests that the brain–gut–microbiota axis plays a crucial role in depression-like phenotypes (Chevalier et al., 2020; Siopi et al., 2020, 2017b). Rodents with depression-like behaviors induced by stress have been demonstrated to have abnormal levels of gut microbiota-related SCFAs and other metabolites such as alanine, isoleucine, L-threonine, serine and tyrosine, which may be associated with depressive-like phenotypes and altered

levels of 5-HT in the brain (Li et al., 2019a; Wu et al., 2020).

Research demonstrating that administration of microbiota or their metabolites can cause or rescue depression-like phenotypes suggests a bidirectional regulatory effect of the brain–gut–microbiota axis on depression. In some studies, fecal samples containing microbial communities were obtained from patients with depression or mice with depression-like behaviors. Subsequently, fecal microbiota transplantation (FMT) of the "depression-related microbiome" caused depressive-like phenotypes in rodents compared with controls (Knudsen et al., 2021; Wang et al., 2020b). In contrast, treatment with a mixture of SCFAs, including acetate, butyrate, and propionate, has been shown to alleviate stress-induced depressive-like behaviors in mice (van de Wouw et al., 2018).

A recent iTRAQ (Isobaric Tag for Relative and Absolute Quantitation)-based proteomics analysis conducted on a mouse model of depression caused by FMT from depressed patients identified protein alterations in serum, prefrontal cortex, cecum, and liver (Liu et al., 2021). The microbiota-driven protein profile was dramatically altered in these tissues, and the altered protein profiles were predicted to play roles in the inflammatory immune response and metabolic regulation, which may contribute to depression via the gut–brain axis (Liu et al., 2021). A better understanding of marked alterations from the gut to brain, or from the brain to gut, can strengthen evidence of the role of the brain–gut axis in depression (Jiang et al., 2015; Naseribafrouei et al., 2014; Park et al., 2013; Tillmann et al., 2019; Yang et al., 2020a; Zheng et al., 2016, 2020b) (Fig. 2).

3.2. Findings from depressed patients

Numerous clinical studies have reported abnormal composition of the gut microbiota in patients with depression compared to healthy controls, further suggesting a role of the brain–gut–microbiota axis in depression (Jiang et al., 2015; Naseribafrouei et al., 2014; Park et al., 2013; Tillmann et al., 2019; Yang et al., 2020a; Zheng et al., 2016, 2020b). One such study also found that gut microbiota dysbiosis in depressed patients was associated with reduced BDNF levels and that *Faecalibacterium* was related to clinician-related depression scale score, contributing to the severity of depressive symptoms (Jiang et al., 2015). A recent study found that gut microbiota DNA contributes to the depression phenotype in distinguishing depressed patients from controls, as shown by machine learning targeting single nucleotide exact amplicon sequence variants in patients' gut microbiome (Stevens et al., 2021). An in-depth study involving depressed patients adopted a multilevel omics perspective to understand alterations in the gut microbiome and metabolomics as contributors to gut ecology in the pathogenesis of depression (Yang et al., 2020a). The overall phenotype of gut ecology, including 3 bacteriophages, 47 bacterial species, and 50 fecal metabolites, in depressed patients differed significantly from that of healthy controls. The altered gut microbiota and metabolites in depressed patients included *Blautia sp. Marseille-P2398*, *Blautia wexlerae*, *Ruminococcus sp. 5_1_39BFAA*, *Oscillibacter sp. ER4*, phosphate, and L-homoserine, which may be important markers of depression (Yang et al., 2020a). A study of depression and bipolar disorder also noted a distinctly different composition of the gut microbiota in patients compared with healthy controls (Zheng et al., 2020b). Depression was associated with major changes in the family level of *Bacteroidaceae*, while the family levels of *Lachnospiraceae, Prevotellaceae,* and *Ruminococcaceae* mainly contributed to bipolar disorder (Zheng et al., 2020b).

Several systematic reviews and meta-analyses have been conducted to evaluate the evidence of gut microbiota perturbations in patients with depression. One meta-analysis showed that the genera *Corprococcus* and *Faecalibacterium* were decreased in depressed patients compared to non-
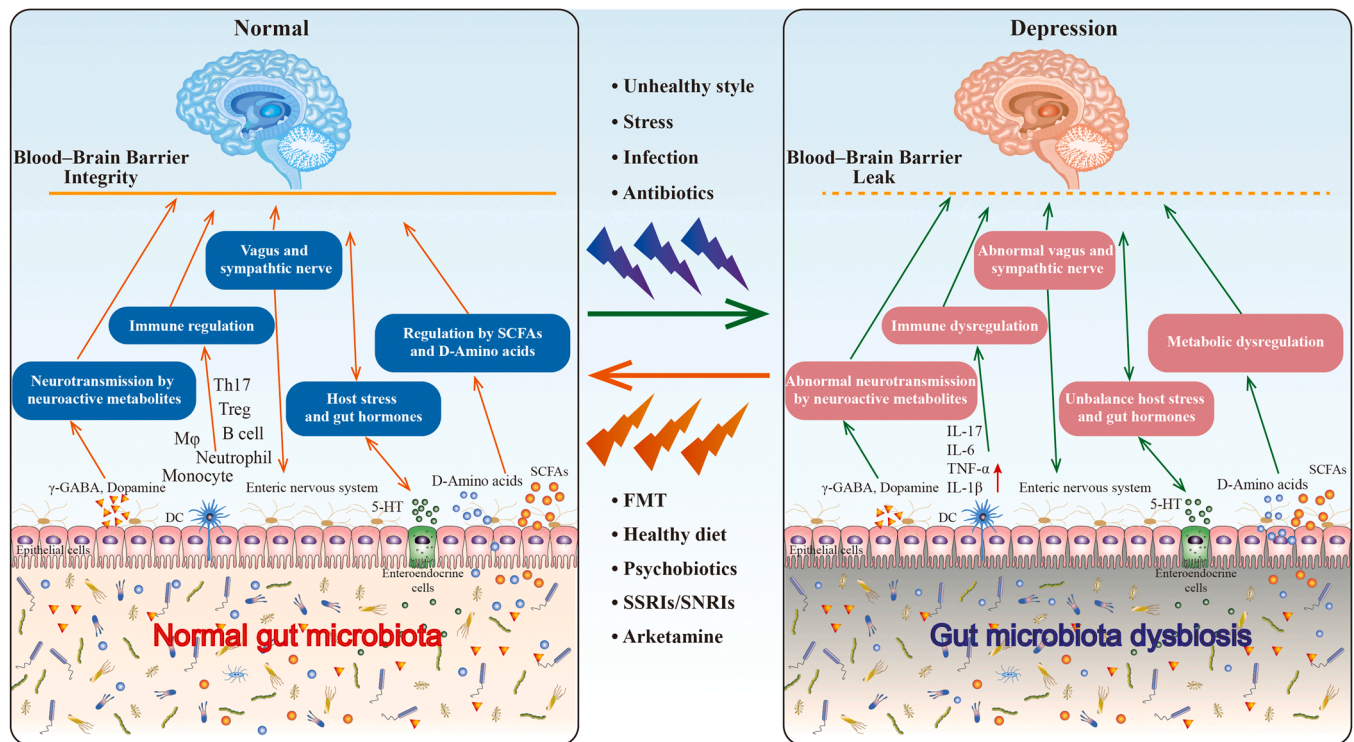
Fig. 2. The role of the brain–gut–microbiota axis in depression. An unhealthy lifestyle due to increased and sustained stress, infection, or other factors can cause dysbiosis of the gut microbiota. Abnormal conditions in the body may be bidirectionally regulated by the brain–gut–microbiota axis via neural signals, immune signals, or chemical signal, thereby contributing to depression. Research has demonstrated that fecal microbiota transplantation (FMT), diet, psychobiotics, and antidepressants (e.g., SSRIs, SNRIs, arketamine) can restore abnormalities in the gut microbiota, abnormal brain function, and depressive symptoms via the brain–gut–microbiota axis. CNS: central nervous system, DC: dendritic cell, 5-HT: 5-hydroxytryptamine, IL-6: interleukin 6, IL-17: interleukin 17, IL-1β: interleukin 1β, SCFA: short chain fatty acid, TNF-α: tumor necrosis factor α. With slight modifications from the articles (Cenit et al., 2017; Wei et al., 2021).

depressed controls, and that depressive symptoms improved in interventional studies with probiotics (Sanada et al., 2020). Another recent meta-analysis showed that gut microbiota perturbations were associated with a transdiagnostic pattern with depletion of certain anti-inflammatory butyrate-producing bacteria and enrichment of pro-inflammatory bacteria in patients with psychiatric disorders including depression (Nikolova et al., 2021). A better understanding of marked alterations from gut to brain or from brain to gut will ascertain the role of the brain–gut axis in patients with depression (Fig. 2).

3.3. Role of the vagus nerve in depression

Crosstalk between the brain and gut microbiota is regulated through various routes including the vagus nerve, immune system, and ENS (Bonaz et al., 2018; Cawthon and de La Serre, 2018; Cryan et al., 2019; Forsythe et al., 2014). The vagus nerve acts as a connection among the brain, gut microbiota, and immune system (Liu and Forsythe, 2021). Depression is associated with vagus nerve signaling, which is implicated in inflammatory regulation and modulation by neuroactive molecules (Breit et al., 2018).

In 2011, Bravo et al. (2011) reported that oral gavage with *Lactobacillus rhamnosus* attenuated stress-induced depression-like behaviors in mice compared with controls, and that vagotomy blocked the effects of *Lactobacillus rhamnosus* in brain chemistry and depression-like behaviors. We previously reported that subdiaphragmatic vagotomy (SDV) attenuated depression-like behaviors, higher levels of pro-inflammatory cytokines [i.e., interleukin-6 (IL-6) and tumor necrosis factor (TNF-α)], decreased expression of synaptic proteins, and abnormal composition of the gut microbiota in mice after administration of LPS (Zhang et al., 2020a). Furthermore, ingestion of "depression-related" microbes (*Lactobacillus intestinalis* and *Lactobacillus reuteri*) led to depression-like phenotypes, higher plasma IL-6 levels, and decreased expression of synaptic proteins in the prefrontal cortex (PFC) of antibiotic-treated mice (Wang et al., 2020b). Interestingly, SDV blocked the development of depression-like behaviors, elevation of plasma IL-6 levels, and downregulation of synaptic proteins in the PFC after ingestion of these two microbes.

The α7 nicotinic acetylcholine receptor (nAChR) plays a key role in the cholinergic immune system in the brain and periphery (Hashimoto, 2015b; Rosas-Ballina and Tracey, 2009; Wang et al., 2003). We previously reported that α7 nAChR knock-out (KO) resulted in depression-like behaviors via systemic inflammation (Zhang et al., 2016). Another study reported that FMT from α7 nAChR KO mice with depression-like phenotypes caused depression-like phenotypes in antibiotic-treated mice, and that SDV blocked these depression-like behaviors after FMT (Pu et al., 2021). Furthermore, we reported that FMT from CSDS susceptible mice caused a depression-like phenotype in antibiotic-treated wildtype mice and resilient *Ephx2* KO mice, suggesting that the depression-related microbiome contributes to the conversion of resilient *Ephx2* KO mice into KO mice with depression-like phenotypes (Wang et al., 2021). SDV was also shown to block the development of depression-like phenotypes after ingestion of depression-related microbiome. Collectively, these findings support that the vagus nerve is responsible for the functional communication of brain–gut–microbiota axis in depression, resulting in depression-like phenotypes.

In contrast, the vagus nerve may not play a role in gut–brain communication during social stress since social activity and corticosterone levels in SDV-operated antibiotic-treated mice were not significantly different than those in sham-operated antibiotic-treated mice (Wu et al., 2021b). It should be noted that the surgical vagotomy procedure has limitations for differentiating afferent from peripheral signal input to the brain, or efferent from CNS output to a peripheral organ like the gut, thereby contributing to alterations in immune response, brain function, or behavior (Liu and Forsythe, 2021).

Mouse models of depression have been employed to study neuronal activity in response to *Lactobacillus rhamnosus (JB-1)* treatment. One study found that alterations in c-Fos protein in brain regions were associated with vagal signaling in a dependent or independent manner (Bharwani et al., 2020). Given such findings, there is great interest in identifying the precise route of the vagus nerve to the brain–gut–microbiota axis in depression. Seven subtypes of the vagus motor nerve are connected to different peripheral organs by single nucleus RNA-seq in Cre driver mice (Tao et al., 2021). Studies such as this will contribute to further understanding of what kind of vagal motor neuron subtype plays a key role in depression.

4. Immune regulation in depression

Within immune regulation through the brain–gut–microbiota axis, numerous studies have focused on alterations in inflammatory cytokines to investigate the immune response in depression. However, there is a complex immune signal network behind such inflammatory changes, including innate and adaptive immune regulation in the gut, brain, and systemic circulation, which has emerged as part of the communication system of the microbiota, gut, and brain in depression (Cryan et al., 2019; Fung, 2020; Morais et al., 2021; Rudzki and Maes, 2020). For example, dysfunction in the gut–microbiota–immune–brain axis may cause brain damage during neurophysiological development in premature neonates (Seki et al., 2021).

One hypothesis is that the microbiota–gut–immune–glia axis plays a role in depression (Rudzki and Maes, 2020). Erny et al. (2015) reported substantial contributions of the host microbiota to microglia homeostasis, demonstrating that germ-free (GF) mice showed global defects in microglia with altered cell proportions and an immature phenotype, leading to impaired innate immune properties. Notably, recolonization with complex microbiota partially restored microglia features and microbiota-derived SCFAs regulated microglia homeostasis. Glial cells, including microglia, astrocytes, oligodendrocytes, and ependymal cells, interact with neurons to influence brain health and disease, such as depression (Rudzki and Maes, 2020). Glial functions may be driven by the gut microbiota via neural and chemical signal routes. The gut microbiota is of significance to microglial activation states from pro-inflammatory to anti-inflammatory, and microglia dysfunction can trigger signaling cascades of neuroinflammation in depression (Carlessi et al., 2021; Fung et al., 2017; Rudzki and Maes, 2020). For example, rifaximin and minocycline are effective in attenuating depressive-like phenotypes induced by stress; these antidepressant-like effects were associated with microbial composition and metabolites, followed by alteration in brain functions, brain microglia (Iba1), and peripheral inflammatory cytokines [e.g., tumor necrosis factor (TNF)-α, interleukin (IL)− 1β, interferon (IFN)-γ, IL-12] (Li et al., 2021; Schmidtner et al., 2019). Under different pathological states, the gut microbiota can influence other factors — such as dietary regulation, SCFAs, tryptophan metabolism, neurotransmitters like GABA and 5-HT, the hypothalamic pituitary adrenal (HPA) axis, and vagus nerve reflex — to activate microglia and other glia cells (Abdel-Haq et al., 2019; Rudzki and Maes, 2020). We reported significant correlations between microglial markers in the brain and the relative abundance of several bacteria in PLX5622 (colony-stimulating factor 1 receptor inhibitor)-treated mice, suggesting microbiome–microglia crosstalk via the brain–gut axis (Yang et al., 2021). Collectively, these findings suggest that regulation of microglia activation states (M1, M2) via the gut–brain axis may be a promising therapeutic approach for depression (Abdel-Haq et al., 2019; Zhang et al., 2018), since depression may be considered as a microglial disease (Yirmiya et al., 2015).

An increasing number of preclinical and clinical studies suggest that Th17 and Treg cells make a significant contribution to depression (Beurel et al., 2013; Beurel and Lowell, 2018; Ghosh et al., 2022; Kim et al., 2021; Li et al., 2010; Poletti et al., 2017; Schiweck et al., 2020; Sun et al., 2020a). Intestinal Th17 and Treg cells are regulated by the gut microbiota, while brain-related Th17 and Treg cells maintain immune homeostasis for controlling neuroinflammation, microglia activation,

astrocyte activation, and brain development during pregnancy (Bauer and Teixeira, 2021; Beurel and Lowell, 2018; Carlessi et al., 2021; Osborne et al., 2019; Pandiyan et al., 2019). Notably, an imbalance between Th17 and Treg cells, or the ratio of Th17/Treg cells, has been reported to play a critical role in depression. Th17/Treg cells are specifically required for regulation of the brain–gut–microbiota axis in brain neuroinflammation (Grosse et al., 2016; Hong et al., 2013; Medina-Rodriguez et al., 2020; Schiweck et al., 2020; Westfall et al., 2021a). Imbalance between Th17 and Treg cells regulated by the gut microbiota could confer resilience versus susceptibility to stress (Ambree et al., 2019; Westfall et al., 2021a, 2021b), and may be involved in the antidepressant effect and side effects of ketamine (Cui et al., 2021). Specific gut microbiota, such as segmented filamentous bacteria, *Clostridia, Bacteroides fragilis, Lactobacillus reuteri,* and *Bifidobacterium*, as well as their metabolites like SCFAs and ATP, are also involved in Th17/Treg activity, thereby shaping the imbalance between Th17 and Treg cells (Cheng et al., 2019; Zhu et al., 2020). Further studies are needed to identify the interrelationship between the gut microbiota and Th17/Treg cells in depression to understand the brain–gut–microbiota axis in the immune signal network.

5. SCFAs and D-amino acids

SCFAs have become one of the most studied classes of small molecules in recent years due to their essential role in gut microbiota metabolism. In addition to maintaining intestinal homeostasis (van der Hee and Wells, 2021), SCFAs can shed light on why dysbiosis in the gut microbiota is involved in the pathophysiology of depression via brain–gut signals (Dalile et al., 2019; Silva et al., 2020; Wu et al., 2020). For example, the levels of acetic acid, propionic acid, and pentanoic acid are altered in the chronic restraint stress (CRS) model of depression, and mice with a depression-like phenotype show a significant decrease associated with gut microbiota dysbiosis and neurotransmitters such as 5-HT and its metabolite 5-hydroxyindoleacetic acid (5-HIAA) compared with controls (Wu et al., 2020). A comparison study of depressed patients and healthy controls found that depressed patients showed decreased butyrate (anti-inflammatory properties) produced by *Faecalibacterium* and increased LPS (pro-inflammatory properties) produced by *Flavonifractor* (Liu et al., 2020).

A recent systematic review of 26 studies of anxiety disorder and depression concluded that pro-inflammatory species, such as *Enterobacteriaceae* and *Desulfovibrio,* are higher whereas SCFAs related to *Faecalibacterium* are lower in patients compared with controls (Simpson et al., 2021). It has been suggested that butyrate and other SCFAs may improve depression-like behaviors through their anti-inflammatory effects, inducing histone hyperacetylation and elevating BDNF levels (Stilling et al., 2016).

SCFAs can regulate BBB permeability and cross the BBB, thereby affecting neurons and immune cell crosstalk that contributes to brain function and behavior (Agirman and Hsiao, 2021; Dalile et al., 2019; Silva et al., 2020; Xiao et al., 2020). Treatment with a mixture of acetic acid, propionic acid, and butyric acid improved permeability of the intestinal barrier induced by chronic stress (van de Wouw et al., 2018). Non-absorbable antibiotic rifaximin targeting the brain–gut–microbiota axis was shown to improve depressive-like behavior caused by chronic unpredictable mild stress (CUMS) (Li et al., 2021). The antidepressant-like effect of rifaximin was reflected by inhibition of microglia activation in phagocytosis and increase of butyric acid levels in the brain, which were associated with the gut microbiota taxa *Ruminococcus bromii* and *Lachnospiraceae* (Li et al., 2021). Butyrate treatment also ameliorated LPS-induced depression-like phenotype through anti-inflammation (Yamawaki et al., 2018). Understanding the neuroactive potential of SCFAs involved in host health and disease may involve other routes targeting the brain–gut–microbiota axis. For example, SCFA-induced depression may be related to Th17/Treg cells immune regulation (Westfall et al., 2021b), TLR4/NF-κB-mediated

inflammatory response (Sun et al., 2020b), tryptophan catabolites metabolism (Chen et al., 2021), and the endocannabinoid system (Chevalier et al., 2020; Vijay et al., 2021). Taken together, these studies support that SCFAs play various crucial roles in the brain–gut–microbiota axis and may be a novel therapeutic target for depression (Merchak and Gaultier, 2020).

At present, the precise mechanisms underlying the role of the brain–gut–microbiota axis in depression are unclear. It is difficult to definitively show how many or what key routes are responsible for the pathophysiology of depression. Nevertheless, the brain–gut–microbiota axis is a promising therapeutic target for depression.

It has been suggested that gut microbiome can produce free D-amino acids such as D-serine and D-glutamate (Chang et al., 2020; Matsumoto et al., 2018; Nakade et al., 2018; Sasabe and Suzuki, 2018). A study using high-sensitivity liquid chromatography-tandem mass spectrometry showed that 12 free D-amino acids (D-alanine, D-arginine, D-aspartate, D-glutamine, D-glutamate, D-*allo*-isoleucine, D-leucine, D-lysine, D-methionine, D-phenylalanine, D-serine, D-tryptophan) could be produced by intestinal microbiota (Matsumoto et al., 2018). Accumulating evidence suggests that D-amino acids such as D-serine and D-glutamate might play a role in the pathophysiology of a number of neuropsychiatric disorders including depression, schizophrenia, and Alzheimer's disease (Chang et al., 2021; Dong et al., 2018; Fujita et al., 2016; Hashimoto et al., 2003, 2004, 2005, 2016; Yamada et al., 2005). However, the precise roles of D-amino acids and gut microbiota in neuropsychiatric disorders such as depression are unknown. Further detail study is needed to investigate how gut microbiome-derived D-amino acids play a role in health and diseases in the host.

6. Targeting the brain–gut–microbiota for depression

6.1. FMT

A brief review of the history of FMT is helpful for understanding the implications of the brain–gut–microbiota axis in depression. A milestone study by Sudo et al. (2004) compared the brain–gut–microbiota axis among GF, specific pathogen free (SPF,) and gnotobiotic mice, reporting that GF mice had a high level of plasma adrenocorticotropic hormone (ACTH) and corticosterone, and a low level of BDNF in brain regions, within a model of HPA response to restraint stress. In contrast, *Bifidobacterium (B.) infantis* or colonizing microbes with SPF mice feces showed a reversal effect in response to HPA stress (Sudo et al., 2004). Several years later, Bercik et al. (2011) reported that the gut microbiota affected brain BDNF levels and exploratory behavior in antibiotic-induced dysbiosis model mice, and that these alterations were reversed following withdrawal of antimicrobials. Importantly, the authors also demonstrated that the brain–gut–microbiota axis was regulated by FMT: the gut microbiota of NIH (National Institute of Health) Swiss mice colonized inside GF BALB/c mice increased brain BDNF level and exploratory behavior, while the gut microbiota of BALB/c mice colonized inside GF NIH Swiss mice decreased exploratory behavior (Bercik et al., 2011).

Fei and Zhao (2013) reported that disease-related phenotypes can be transmitted from one individual to another by FMT, such that recipient mice displayed phenotypes of obesity and insulin resistance after being transplanted with the gut microbiota of *Enterobacter* from morbidly obese humans, accompanied by serum endotoxin and inflammatory cytokines increases. A randomized controlled trial showed that intestinal flora from lean donors restored insulin sensitivity and increased bacterial diversity in obese patients with metabolic syndrome, and that this effect may be regulated by microbiota-derived butyrate (Vrieze et al., 2012). These findings strongly suggest that microbiota have systemic functions in transferring the host phenotypes to other individuals via the whole microbiota, specific microorganisms, or microbiota-related metabolites (Koh and Backhed, 2020).

Reconstitution with microbes or FMT may be an effective

intervention for various brain diseases. A review article highlighted the utility of FMT as a therapeutic option for depression (Koh and Backhed, 2020). As detailed above, depressive-like phenotypes can be transferred from mice with depression-like phenotypes or depressed patients via FMT, suggesting that FMT may have beneficial effects for improving depression (Kelly et al., 2016; Knudsen et al., 2021; Li et al., 2019c; Marcondes Avila et al., 2020; Pu et al., 2021; Rao et al., 2021a, 2021b; Wang et al., 2020a; Wang et al., 2020b; Zhang et al., 2019b; Zheng et al., 2016). Various case reports, meta-analyses, and systematic reviews have also showed that FMT improves depressive symptoms in patients with depression (Cai et al., 2019; Chinna Meyyappan et al., 2020; Cooke et al., 2021; Evrensel and Tarhan, 2021; Fond et al., 2020; Green et al., 2021; Hinton, 2020; Settanni et al., 2021; Xu et al., 2021). However, it is difficult to draw definitive conclusions from FMT clinical trials of patients with depression because short-term and long-term adverse events of FMT cannot be avoided or determined in the context of current FMT therapeutic strategies (Baunwall et al., 2021; Merrick et al., 2020).

6.2. Diet for depression

Epidemiological evidence suggests that the effects of diet on depression may be relevant to the stage of life including prenatal depression (Marx et al., 2019). Systematic reviews and meta-analyses have concluded that healthy dietary interventions have beneficial effects on both prevention and improvement in depression (Lassale et al., 2019; Wu et al., 2021a). A large-scale metagenomics study of 1054 volunteers confirmed that there is a close relationship among intestinal microbes, dietary health, and depression (Valles-Colomer et al., 2019). Butyric acid-producing *Faecalibacterium* and *Coprococcus bacteria* were identified as important indicators of a high-quality diet, even in patients with depression treated with antidepressants (Valles-Colomer et al., 2019). Using machine learning strategies in the American Gut Project, host variables such as diet were identified as important variables contributing to the human gut microbiota (Vujkovic-Cvijin et al., 2020). In light of these findings, a low-quality diet is thought to trigger a series of reactions that include changing intestinal microbiota diversity, reducing essential nutrient intake, reducing the growth substrates of specific microorganisms, and further aggravating dysbiosis of gut microbial communities in patients with depression (Dinan et al., 2019).

A Western diet high in saturated fat and sugars has been shown to have a deleterious impact on neuropsychological outcomes, increase endotoxin production from commensal bacteria, and promote neuroinflammation and BBB leakage, thereby leading to cognitive decline and depression (Dinan et al., 2019; Noble et al., 2017; Psaltopoulou et al., 2013). A high fructose diet treatment in mice lasting for several weeks led to neuroinflammatory alteration in the hippocampus, mediated by the NLRP6 inflammasome impairing the intestinal epithelial barrier, and SCFA supplementation ameliorated neuroinflammation caused by this high fructose diet (Li et al., 2019b). Adult rats treated with a high-fat diet for 3 weeks showed depression-like behavior and a low level of BDNF-TrkB signaling in brain regions (frontal cortex and hippocampus), although there were no data indicating gut microbiota dysfunction (Sharma et al., 2012). The ability of a high-fat diet to induce a depression-like phenotype may relate to hypothalamic PKA (protein kinase A) signaling and leptin/LepRb (leptin receptor) signaling (Vagena et al., 2019; Yang et al., 2016b). Negative emotions can affect our eating behavior and energy intake by promoting high calorie food intake and hedonistic eating, which are related to neuropeptide Y in the brain (Herzog, 2020). In contrast, healthy eating patterns like the Mediterranean diet have been shown to increase gut microbial taxa and reduce inflammation markers, thus contributing to improvement in depressive symptoms (Firth et al., 2020). In addition, Norwegian and Japanese diets; omega-3 polyunsaturated fatty acids (PUFAs) enriched foods; and healthy dietary patterns involving a combination of high intake of whole grains, olive oil, vegetables, fruits, fish, soy, and lower fat dairy may be associated with a lower risk of depression (Deacon

et al., 2017; Lassale et al., 2019; Nishi et al., 2020; Okubo et al., 2019; Opie et al., 2017). Given such findings, diets targeting the brain–gut–microbiota axis have been suggested to benefit the gut microbiota, promote a healthier microbiome, maintain the integrity of the intestinal barrier, and contribute to brain development (Lassale et al., 2019; Silva et al., 2020; Zhang and Kutateladze, 2018; Zheng et al., 2020a).

6.3. Psychobiotics for depression

Given accumulating evidence for the existence of the brain–gut–microbiota axis and its potential implications in psychiatric disorders, the concept of psychobiotics was proposed in 2013. Psychobiotics are considered a class of probiotic that can benefit people suffering from psychiatric disorders, including depression (Dinan et al., 2013). With an expanded scope of probiotic function, psychobiotics mainly include probiotics with adequate amounts of beneficial bacteria and prebiotics with the ability to be utilized by gut microflora to convert beneficial substances (Cunningham et al., 2021; Dinan et al., 2013; Gibson et al., 2017; Sarkar et al., 2016). Psychobiotics targeting the bacteria–gut–brain signals likely involve multiple routes and neural signal networks, such as the ENS and vagus nerve, immune signal network of interactions between microbe-associated molecular patterns and PRRs like TLRs, C-type lectins and inflammasomes, and gut microbiota-derived SCFAs (Sarkar et al., 2016). A recent review provides a good summary of the source of probiotics and prebiotics (Cunningham et al., 2021). Probiotics principally include human microbiota, fermented foods, environment-related soil, plants, and animals, whereas prebiotics mainly comprise plants, fungi, animals, microbes, and chemical and physical modification (Cunningham et al., 2021). For example, fructo-oligosaccharides and galacto-oligosaccharides are regarded as prebiotics that exhibit antidepressant and anti-inflammation effects in the chronic stress-induced mouse model of depression (Burokas et al., 2017).

Furthermore, systematic reviews and meta-analysis suggest that psychobiotics have anxiolytic and antidepressant effects (Chudzik et al., 2021; Cohen Kadosh et al., 2021; Dinan et al., 2013; Liu et al., 2019; Smith et al., 2021). Animal studies have confirmed these effects while simultaneously exploring the mechanisms underlying the antidepressant effects of psychobiotics. For example, strain MCC1848 from heat-killed *Lactobacillus helveticus* attenuated depressive-like behaviors induced by subchronic and mild social defeat stress (Maehata et al., 2019). In CUMS model animals, *Bifidobacterium breve CCFM1025* had antidepressant-like effects, as evidenced by improvement in depression-like behavior, reshaping of the gut microbiota community, reduced inflammation, and balancing of HPA axis hyperfunction (Tian et al., 2020). In addition, *CCFM1025* upregulated the BDNF level while downregulating pCREB (cAMP response element-binding protein)-c-Fos signaling in the PFC in response to stress, followed by increased levels of SCFAs and 5-hydroxytryptophan (Tian et al., 2020). Recent reviews and studies on the beneficial effects of psychobiotics for depression have mainly concentrated on the genera *Lactobacillus* and *Bifidobacterium*, finding that different strains have specific contributions to mental health (Barros-Santos et al., 2020; Burnet and Cowen, 2013; Duranti et al., 2020; Misra and Mohanty, 2019; Sarkar et al., 2016). Other psychobiotics have also been found to improve depression. In a CRS mouse model of depression, *Akkermansia muciniphila* was found to ameliorate the depressive-like phenotype by restoring the abnormal gut microbiota and metabolites and by regulating corticosterone, dopamine, and BDNF levels (Ding et al., 2021). Notably, several studies have reported null results for psychobiotics, reporting no improvement in depressive-like behavior (Dinan et al., 2021; Vaghef-Mehrabany et al., 2020). As a result, it is currently difficult to conclude whether psychobiotics have antidepressant effects due to their various modes of action and the possibility of strain-specific effects, multi-strain formulations, or other modalities (Bambury et al., 2018; Vaghef-Mehrabany et al., 2020). Nevertheless,

plant-based psychobiotics targeting the brain–gut–microbiota pathway have been developed and hold high promise as novel antidepressants (Dinan et al., 2021; Vaghef-Mehrabany et al., 2020). Overall, further studies are needed to confirm the beneficial effects of psychobiotics in depression.

6.4. Antidepressants

Antidepressants, such as SNRIs and SSRIs, are the most commonly prescribed drugs for depression despite various side effects, delayed clinical onset, and high non-response rates (Galecki et al., 2018; Hoyer, 2020; Wei et al., 2021). Although the detailed biological mechanisms underlying antidepressant actions remain unclear (Casarotto et al., 2021), recognition of the role of intestinal microbes may be a turning point (Klunemann et al., 2021). An abnormal composition of the gut microbiota is associated with depression (Foster and McVey Neufeld, 2013; Jiang et al., 2015), and antidepressants have anti-microbial and anti-inflammatory effects related to gut microbiota ecological restoration (Galecki et al., 2018; Hashimoto, 2015a; Macedo et al., 2017; McGovern et al., 2019). Various preclinical studies have suggested that SSRIs and other kinds of antidepressants exert anti-microbial activity, and that treatment efficiency may be regulated or governed by microorganisms at multiple taxonomic levels (Ait Chait et al., 2020; Dethloff et al., 2020; Lukic et al., 2019; McVey Neufeld et al., 2019; Ramsteijn et al., 2020; Shen et al., 2021). For example, Duan et al. (2021) reported that the gut microbiota community and metabolites differed significantly between responders and non-responders treated with escitalopram in a CUMS model of depression, with *Prevotellaceae_UCG-003* increasing and *Ruminococcaceae* and *Lactobacillaceae* decreasing in the responder group compared with the non-responder group. Using the same depression model, the antidepressant-like effects of fluoxetine had strong correlations with the gut microbiota, and its antidepressant efficacy was weakened by decreasing 5-HT biosynthesis and disrupting tryptophan metabolism via the gut microbiota (Siopi et al., 2020; Sun et al., 2019). Thus, targeting the brain–gut–microbiota axis could be integrated with antidepressants to achieve better understanding of the neurobiological processes underlying depression (Duan et al., 2021; Harmer et al., 2017; Siopi et al., 2020).

The rapid antidepressant effects of ketamine may also be correlated with the gut microbiota (Hashimoto, 2019, 2020; Wang et al., 2020d; Wei et al., 2021; Wilkowska et al., 2021). (*R*)-ketamine (arketamine) has more potent and longer-lasting antidepressant effects with fewer side effects in rodents and humans compared to (*S*)-ketamine (esketamine) (Bonaventura et al., 2021; Chang et al., 2019; Leal et al., 2021; Yang et al., 2015c; Yao et al., 2021; Zhang et al., 2014, 2020b). However, the precise molecular mechanisms underlying the differential activities of arketamine and esketamine are yet to be fully understood (Hashimoto, 2019, 2020; Heifets et al., 2021; Wei et al., 2020, 2021; Yao et al., 2021). Interestingly, preclinical data suggest that (*R,S*)-ketamine or (*R*)-ketamine has the ability to ameliorate the abnormal composition of gut microbiota associated with depression-like behaviors (Getachew et al., 2018; Huang et al., 2019; Qu et al., 2017; Yang et al., 2017b). The potential role of the brain–gut–microbiota axis in the antidepressant-like action of arketamine is of great interest. In contrast to esketamine, arketamine has specific effects on *Mollicutes* and *Butyricimonas* at different taxonomic levels of the gut microbiota, which are associated with its robust antidepressant-like actions in CSDS susceptible mice (Yang et al., 2017b). In contrast to antidepressant candidate lanicemine, arketamine showed significant antidepressant-like effects in CSDS susceptible mice (Qu et al., 2017). The reason for this difference may be partially due to the restoration of decreased order levels of *Bacteroidales* and *Clostridiales*. The antidepressant-like actions of arketamine may also be associated with gut microbiota alterations at different taxonomic levels, including the family levels of *Ruminococcaceae* and *Mogibacteriaceae* and the genus level of *Clostridium*. Thus, the brain–gut–microbiota axis may be involved in the antidepressant-like effects of (*R,S*)-ketamine

and arketamine (Hashimoto, 2019, 2020; Wei et al., 2021; Wilkowska et al., 2021), although more detailed studies are needed.

7. Conclusions and perspectives

The brain–gut–microbiota axis is a complex and interactive system that includes a neural signal network, immune signal network, and chemical signal network. All of these networks appear to be involved in the pathophysiology of depression. In particular, the vagus nerve, Th17/ Treg activity, microglia, gut microbial composition, and SCFAs have attracted increasing research focus for understanding how the brain–gut–microbiota axis contributes to depression (Fig. 2). The brain–gut–microbiota axis is considered a new paradigm with the potential to provide new treatment strategies for depression (Bambury et al., 2018; Wei et al., 2021). Beneficial effects of diets and psychobiotics targeting the brain–gut–microbiota axis in depression have been increasingly reported in both preclinical and clinical studies (Bambury et al., 2018; Long-Smith et al., 2020; Marx et al., 2021; Simpson et al., 2021). However, the precise mechanisms underlying the role of the brain–gut–microbiota axis in depression remain unclear. Further understanding of the role of the brain–gut–microbiota axis in depression will provide new therapeutic approaches for supporting mental health.

Conflict of interest statement

Dr. Hashimoto is the inventor of filed patent applications on "The use of *R*-Ketamine in the treatment of psychiatric diseases", "(*S*)-norketamine and salt thereof as pharmaceutical", "*R*-Ketamine and derivative thereof as prophylactic or therapeutic agent for neurodegeneration disease or recognition function disorder", "Preventive or therapeutic agent and pharmaceutical composition for inflammatory diseases or bone diseases", "*R*-Ketamine and its derivatives as a preventive or therapeutic agent for a neurodevelopmental disorder", and "Preventive or therapeutic agent and pharmaceutical composition for inflammatory diseases" by the Chiba University. Dr. Hashimoto also declares that he has received research support and consultant from Dainippon Sumitomo, Otsuka, Taisho, Murakami Farm, and Perception Neuroscience. The other authors have no conflict of interest.

References

Abdel-Haq, R., Schlachetzki, J.C.M., Glass, C.K., Mazmanian, S.K., 2019. Microbiome-microglia connections via the gut-brain axis. J. Exp. Med. 216 (1), 41–59. https://doi.org/10.1084/jem.20180794.

Agirman, G., Hsiao, E.Y., 2021. SnapShot: the microbiota-gut-brain axis. Cell 184 (9). https://doi.org/10.1016/j.cell.2021.03.022.

Ait Chait, Y., Mottawea, W., Tompkins, T.A., Hammami, R., 2020. Unravelling the antimicrobial action of antidepressants on gut commensal microbes. Sci. Rep. 10 (1), 17878. https://doi.org/10.1038/s41598-020-74934-9.

Ambree, O., Ruland, C., Zwanzger, P., Klotz, L., Baune, B.T., Arolt, V., Scheu, S., Alferink, J., 2019. Social defeat modulates T helper cell percentages in stress susceptible and resilient mice. Int. J. Mol. Sci. 20 (14), 3512. https://doi.org/10.3390/ijms20143512.

Averina, O.V., Zorkina, Y.A., Yunes, R.A., Kovtun, A.S., Ushakova, V.M., Morozova, A.Y., Kostyuk, G.P., Danilenko, V.N., Chekhonin, V.P., 2020. Bacterial metabolites of human gut microbiota correlating with depression. Int. J. Mol. Sci. 21 (23), 9234. https://doi.org/10.3390/ijms21239234.

Bambury, A., Sandhu, K., Cryan, J.F., Dinan, T.G., 2018. Finding the needle in the haystack: systematic identification of psychobiotics. Br. J. Pharm. 175 (24), 4430–4438. https://doi.org/10.1111/bph.14127.

Barros-Santos, T., Silva, K.S.O., Libarino-Santos, M., Elisangela Gouveia, C.-P., Reis, H.S., Tamura, E.K., de Oliveira-Lima, A.J., Berro, L.F., Uetanabaro, A.P.T., Marinho, E.A. V., 2020. Effects of chronic treatment with new strains of Lactobacillus plantarum on cognitive, anxiety- and depressive-like behaviors in male mice. PLoS One 15 (6), e0234037. https://doi.org/10.1371/journal.pone.0234037.

Bauer, M.E., Teixeira, A.L., 2021. Neuroinflammation in mood disorders: role of regulatory immune cells. Neuroimmunomodulation 28 (3), 99–107. https://doi.org/10.1159/000515594.

Baunwall, S.M.D., Terveer, E.M., Dahlerup, J.F., Erikstrup, C., Arkkila, P., Vehreschild, M.J., Ianiro, G., Gasbarrini, A., Sokol, H., Kump, P.K., et al., 2021. The use of faecal microbiota transplantation (FMT) in Europe: a Europe-wide survey. Lancet Reg. Health Eur. 9, 100181 https://doi.org/10.1016/j.lanepe.2021.100181.

Bercik, P., Denou, E., Collins, J., Jackson, W., Lu, J., Jury, J., Deng, Y., Blennerhassett, P., Macri, J., McCoy, K.D., et al., 2011. The intestinal microbiota affect central levels of brain-derived neurotropic factor and behavior in mice, 609 e591-593 Gastroenterology 141 (2), 599–609. https://doi.org/10.1053/j.gastro.2011.04.052.

Beurel, E., Lowell, J.A., 2018. Th17 cells in depression. Brain Behav. Immun. 69, 28–34. https://doi.org/10.1016/j.bbi.2017.08.001.

Beurel, E., Harrington, L.E., Jope, R.S., 2013. Inflammatory T helper 17 cells promote depression-like behavior in mice. Biol. Psychiatry 73 (7), 622–630. https://doi.org/10.1016/j.biopsych.2012.09.021.

Beurel, E., Toups, M., Nemeroff, C.B., 2020. The bidirectional relationship of depression and inflammation: double trouble. Neuron 107 (2), 234–256. https://doi.org/10.1016/j.neuron.2020.06.002.

Bharwani, A., West, C., Champagne-Jorgensen, K., McVey Neufeld, K.A., Ruberto, J., Kunze, W.A., Bienenstock, J., Forsythe, P., 2020. The vagus nerve is necessary for the rapid and widespread neuronal activation in the brain following oral administration of psychoactive bacteria. Neuropharmacology 170, 108067. https://doi.org/10.1016/j.neuropharm.2020.108067.

Bonaventura, J., Lam, S., Carlton, M., Boehm, M.A., Gomez, J.L., Solis, O., Sanchez-Soto, M., Morris, P.J., Fredriksson, I., Thomas, C.J., et al., 2021. Pharmacological and behavioral divergence of ketamine enantiomers: implications for abuse liability. Mol. Psychiatry 26 (11), 6704–6722. https://doi.org/10.1038/s41380-021-01093-2.

Bonaz, B., Bazin, T., Pellissier, S., 2018. The vagus nerve at the iInterface of the microbiota-gut-brain axis. Front. Neurosci. 12, 49. https://doi.org/10.3389/fnins.2018.00049.

Bravo, J.A., Forsythe, P., Chew, M.V., Escaravage, E., Savignac, H.M., Dinan, T.G., Bienenstock, J., Cryan, J.F., 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 (38), 16050–16055. https://doi.org/10.1073/pnas.1102999108.

Breit, S., Kupferberg, A., Rogler, G., Hasler, G., 2018. Vagus nerve as modulator of the brain-gut axis in psychiatric and inflammatory disorders. Front. Psychiatry 9, 44. https://doi.org/10.3389/fpsyt.2018.00044.

Burnet, P.W., Cowen, P.J., 2013. Psychobiotics highlight the pathways to happiness. Biol. Psychiatry 74 (10), 708–709. https://doi.org/10.1016/j.biopsych.2013.08.002.

Burokas, A., Arboleya, S., Moloney, R.D., Peterson, V.L., Murphy, K., Clarke, G., Stanton, C., Dinan, T.G., Cryan, J.F., 2017. Targeting the microbiota-gut-brain axis: prebiotics have anxiolytic and antidepressant-like effects and reverse the impact of chronic stress in mice. Biol. Psychiatry 82 (7), 472–487. https://doi.org/10.1016/j.biopsych.2016.12.031.

Cai, T., Shi, X., Yuan, L.Z., Tang, D., Wang, F., 2019. Fecal microbiota transplantation in an elderly patient with mental depression. Int. Psychogeriatr. 31 (10), 1525–1526. https://doi.org/10.1017/S1041610219000115.

Carabotti, M., Scirocco, A., Maselli, M.A., Severi, C., 2015. The gut-brain axis: interactions between enteric microbiota, central and enteric nervous systems. Ann. Gastroenterol. 28 (2), 203–209.

Carlessi, A.S., Borba, L.A., Zugno, A.I., Quevedo, J., Reus, G.Z., 2021. Gut microbiota-brain axis in depression: The role of neuroinflammation. Eur. J. Neurosci. 53 (1), 222–235. https://doi.org/10.1111/ejn.14631.

Casarotto, P.C., Girych, M., Fred, S.M., Kovaleva, V., Moliner, R., Enkavi, G., Biojone, C., Cannarozzo, C., Sahu, M.P., Kaurinkoski, K., et al., 2021. Antidepressant drugs act by directly binding to TRKB neurotrophin receptors. Cell 184 (5), 1299–1313. https://doi.org/10.1016/j.cell.2021.01.034.

Caspani, G., Kennedy, S., Foster, J.A., Swann, J., 2019. Gut microbial metabolites in depression: understanding the biochemical mechanisms. Microb. Cell 6 (10), 454–481. https://doi.org/10.15698/mic2019.10.693.

Cawthon, C.R., de La Serre, C.B., 2018. Gut bacteria interaction with vagal afferents. Brain Res. 1693 (part B), 134–139. https://doi.org/10.1016/j.brainres.2018.01.012.

Cenit, M.C., Sanz, Y., Codoñer-Franch, P., 2017. Influence of gut microbiota on neuropsychiatric disorders. World J. Gastroenterol. 23 (30), 5486–5498. https://doi.org/10.3748/wjg.v23.i30.5486.

Chang, C.H., Lin, C.H., Lane, H.Y., 2020. D-glutamate and gut microbiota in Alzheimer's disease. Int. J. Mol. Med. 21 (8), 2676. https://doi.org/10.3390/ijms21082676.

Chang, C.H., Lin, C.H., Liu, C.Y., Huang, C.S., Chen, S.J., Lin, W.C., Yang, H.T., Lane, H.Y., 2021. Plasma D-glutamate levels for detecting mild cognitive impairment and Alzheimer's disease: Machine learning approaches. J. Psychopharmacol. 35 (3), 265–272. https://doi.org/10.1177/0269881120972331.

Chang, L., Zhang, K., Pu, Y., Qu, Y., Wang, S.M., Xiong, Z., Ren, Q., Dong, C., Fujita, Y., Hashimoto, K., 2019. Comparison of antidepressant and side effects in mice after intranasal administration of (R,S)-ketamine, (R)-ketamine, and (S)-ketamine. Pharmacol. Biochem. Behav. 181, 53–59. https://doi.org/10.1016/j.pbb.2019.04.008.

Chen, L.M., Bao, C.H., Wu, Y., Liang, S.H., Wang, D., Wu, L.Y., Huang, Y., Liu, H.R., Wu, H.G., 2021. Tryptophan-kynurenine metabolism: a link between the gut and brain for depression in inflammatory bowel disease. J. Neuroinflamm. 18 (1), 135. https://doi.org/10.1186/s12974-021-02175-2.

Cheng, H., Guan, X., Chen, D., Ma, W., 2019. The Th17/Treg cell balance: a gut microbiota-modulated story. Microorganisms 7 (12), 583. https://doi.org/10.3390/microorganisms7120583.

Chevalier, G., Siopi, E., Guenin-Mace, L., Pascal, M., Laval, T., Rifflet, A., Boneca, I.G., Demangel, C., Colsch, B., Pruvost, A., et al., 2020. Effect of gut microbiota on depressive-like behaviors in mice is mediated by the endocannabinoid system. Nat. Commun. 11 (1), 6363. https://doi.org/10.1038/s41467-020-19931-2.

Chinna Meyyappan, A., Forth, E., Wallace, C.J.K., Milev, R., 2020. Effect of fecal microbiota transplant on symptoms of psychiatric disorders: a systematic review. BMC Psychiatry 20 (1), 299. https://doi.org/10.1186/s12888-020-02654-5.

Chudzik, A., Orzylowska, A., Rola, R., Stanisz, G.J., 2021. Probiotics, prebiotics and postbiotics on mitigation of depression symptoms: modulation of the brain-gut-microbiome axis. Biomolecules 11 (7), 1000. https://doi.org/10.3390/biom11071000.

Codagnone, M.G., Spichak, S., O'Mahony, S.M., O'Leary, O.F., Clarke, G., Stanton, C., Dinan, T.G., Cryan, J.F., 2019. Programming bugs: microbiota and the developmental origins of brain health and disease. Biol. Psychiatry 85 (2), 150–163. https://doi.org/10.1016/j.biopsych.2018.06.014.

Cohen Kadosh, K., Basso, M., Knytl, P., Johnstone, N., Lau, J.Y.F., Gibson, G.R., 2021. Psychobiotic interventions for anxiety in young people: a systematic review and meta-analysis, with youth consultation. Transl. Psychiatry 11 (1), 352. https://doi.org/10.1038/s41398-021-01422-7.

Cooke, N.C.A., Bala, A., Allard, J.P., Hota, S., Poutanen, S., Taylor, V.H., 2021. The safety and efficacy of fecal microbiota transplantation in a population with bipolar disorder during depressive episodes: study protocol for a pilot randomized controlled trial. Pilot Feasibility Stud. 7 (1), 142. https://doi.org/10.1186/s40814-021-00882-4.

COVID-19 Mental Disorders Collaborators, 2021. Global prevalence and burden of depressive and anxiety disorders in 204 countries and territories in 2020 due to the COVID-19 pandemic. Lancet 398 (10312), 1700–1712. https://doi.org/10.1016/S0140-6736(21)02143-7.

Cryan, J.F., O'Riordan, K.J., Cowan, C.S.M., Sandhu, K.V., Bastiaanssen, T.F.S., Boehme, M., Codagnone, M.G., Cussotto, S., Fulling, C., Golubeva, A.V., et al., 2019. The Microbiota-gut-brain axis. Physiol. Rev. 99 (4), 1877–2013. https://doi.org/10.1152/physrev.00018.2018.

Cui, M., Dai, W., Kong, J., Chen, H., 2021. Th17 cells in depression: are they crucial for the antidepressant effect of ketamine? Front. Pharmacol. 12, 649144 https://doi.org/10.3389/fphar.2021.649144.

Cunningham, M., Azcarate-Peril, M.A., Barnard, A., Benoit, V., Grimaldi, R., Guyonnet, D., Holscher, H.D., Hunter, K., Manurung, S., Obis, D., et al., 2021. Shaping the future of probiotics and prebiotics. Trends Microbiol. 29 (8), 667–685. https://doi.org/10.1016/j.tim.2021.01.003.

Dalile, B., Van Oudenhove, L., Vervliet, B., Verbeke, K., 2019. The role of short-chain fatty acids in microbiota-gut-brain communication. Nat. Rev. Gastroenterol. Hepatol. 16 (8), 461–478. https://doi.org/10.1038/s41575-019-0157-3.

Deacon, G., Kettle, C., Hayes, D., Dennis, C., Tucci, J., 2017. Omega 3 polyunsaturated fatty acids and the treatment of depression. Crit. Rev. Food Sci. Nutr. 57 (1), 212–223. https://doi.org/10.1080/10408398.2013.876959.

Dethloff, F., Vargas, F., Elijah, E., Quinn, R., Park, D.I., Herzog, D.P., Muller, M.B., Gentry, E.C., Knight, R., Gonzalez, A., et al., 2020. Paroxetine administration affects microbiota and bile acid levels in mice. Front. Psychiatry 11, 518. https://doi.org/10.3389/fpsyt.2020.00518.

Dinan, T.G., Cryan, J.F., 2013. Melancholic microbes: a link between gut microbiota and depression? Neurogastroenterol. Motil. 25 (9), 713–719. https://doi.org/10.1111/nmo.12198.

Dinan, T.G., Stanton, C., Cryan, J.F., 2013. Psychobiotics: a novel class of psychotropic. Biol. Psychiatry 74 (10), 720–726. https://doi.org/10.1016/j.biopsych.2013.05.001.

Dinan, T.G., Stanton, C., Long-Smith, C., Kennedy, P., Cryan, J.F., Cowan, C.S.M., Cenit, M.C., van der Kamp, J.W., Sanz, Y., 2019. Feeding melancholic microbes: MyNewGut recommendations on diet and mood. Clin. Nutr. 38 (5), 1995–2001. https://doi.org/10.1016/j.clnu.2018.11.010.

Dinan, T.G., Butler, M.I., Cryan, J.F., 2021. Psychobiotics: evolution of novel antidepressants. Mod. Trends Psychiatry 32, 134–143. https://doi.org/10.1159/000510424.

Ding, Y., Bu, F., Chen, T., Shi, G., Yuan, X., Feng, Z., Duan, Z., Wang, R., Zhang, S., Wang, Q., et al., 2021. A next-generation probiotic: *Akkermansia muciniphila* ameliorates chronic stress-induced depressive-like behavior in mice by regulating gut microbiota and metabolites. Appl. Microbiol. Biotechnol. 105 (21–22), 8411–8426. https://doi.org/10.1007/s00253-021-11622-2.

Dong, C., Zhang, J.C., Ren, Q., Ma, M., Qu, Y., Zhang, K., Yao, W., Ishima, T., Mori, H., Hashimoto, K., 2018. Depletion of serine racemase confers D-serine-dependent resilience to chronic social defeat stress. Neurochem. Int. 116, 43–51. https://doi.org/10.1016/j.neuint.2018.03.008.

Douglas, G.M., Bielawski, J.P., Langille, M.G.I., 2020. Re-evaluating the relationship between missing heritability and the microbiome. Microbiome 8 (1), 87. https://doi.org/10.1186/s40168-020-00839-4.

Duan, J., Huang, Y., Tan, X., Chai, T., Wu, J., Zhang, H., Li, Y., Hu, X., Zheng, P., Ji, P., et al., 2021. Characterization of gut microbiome in mice model of depression with divergent response to escitalopram treatment. Transl. Psychiatry 11 (1), 303. https://doi.org/10.1038/s41398-021-01428-1.

Duranti, S., Ruiz, L., Lugli, G.A., Tames, H., Milani, C., Mancabelli, L., Mancino, W., Longhi, G., Carnevali, L., Sgoifo, A., et al., 2020. *Bifidobacterium adolescentis* as a key member of the human gut microbiota in the production of GABA. Sci. Rep. 10 (1), 14112. https://doi.org/10.1038/s41598-020-70986-z.

Erny, D., Hrabě de Angelis, A.L., Jaitin, D., Wieghofer, P., Staszewski, O., David, E., Keren-Shaul, H., Mahlakoiv, T., Jakobshagen, K., Buch, T., et al., 2015. Host microbiota constantly control maturation and function of microglia in the CNS. Nat. Neurosci. 18 (7), 965–977. https://doi.org/10.1038/nn.4030.

Evrensel, A., Tarhan, K.N., 2021. Emerging role of gut-microbiota-brain axis in depression and therapeutic implication. Prog. Neuropsychopharmacol. Biol. Psychiatry 106, 110138. https://doi.org/10.1016/j.pnpbp.2020.110138.

Fei, N., Zhao, L., 2013. An opportunistic pathogen isolated from the gut of an obese human causes obesity in germfree mice. ISME J. 7 (4), 880–884. https://doi.org/10.1038/ismej.2012.153.

Firth, J., Gangwisch, J.E., Borisini, A., Wootton, R.E., Mayer, E.A., 2020. Food and mood: how do diet and nutrition affect mental wellbeing? BMJ 369, m2382. https://doi.org/10.1136/bmj.m2382.

Fond, G.B., Lagier, J.C., Honore, S., Lancon, C., Korchia, T., Sunhary De Verville, P.L., Llorca, P.M., Auquier, P., Guedj, E., Boyer, L., 2020. Microbiota-orientated treatments for major depression and schizophrenia. Nutrients 12 (4), 1024. https://doi.org/10.3390/nu12041024.

Forsythe, P., Bienenstock, J., Kunze, W.A., 2014. Vagal pathways for microbiome-brain-gut axis communication. Adv. Exp. Med. Biol. 817, 115–133. https://doi.org/10.1007/978-1-4939-0897-4_5.

Foster, J.A., McVey Neufeld, K.A., 2013. Gut-brain axis: How the microbiome influences anxiety and depression. Trends Neurosci. 36 (5), 305–312. https://doi.org/10.1016/j.tins.2013.01.005.

Friedrich, M.J., 2017. Depression is the leading cause of disability around the world. JAMA 317 (15), 1517. https://doi.org/10.1001/jama.2017.3826.

Fujita, Y., Ishima, T., Hashimoto, K., 2016. Supplementation with D-serine prevents the onset of cognitivde deficits in adult offspring after maternal immune activation. Sci. Rep. 6, 37261. https://doi.org/10.1038/srep37261.

Fung, T.C., 2020. The microbiota-immune axis as a central mediator of gut-brain communication. Neurobiol. Dis. 136, 104714 https://doi.org/10.1016/j.nbd.2019.104714.

Fung, T.C., Olson, C.A., Hsiao, E.Y., 2017. Interactions between the microbiota, immune and nervous systems in health and disease. Nat. Neurosci. 20 (2), 145–155. https://doi.org/10.1038/nn.4476.

Galecki, P., Mossakowska-Wojcik, J., Talarowska, M., 2018. The anti-inflammatory mechanism of antidepressants - SSRIs, SNRIs. Prog. Neuropsychopharmacol. Biol. Psychiatry 80 (Pt C), 291–294. https://doi.org/10.1016/j.pnpbp.2017.03.016.

Ganz, J., 2021. Revealing the complexity of the gut's brain. Nat. Neurosci. 24 (1), 1–2. https://doi.org/10.1038/s41593-020-00769-2.

GBD, 2019. Disease and Injuries Collaborators, 2020. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet 396 (10258), 1204–1222. https://doi.org/10.1016/S0140-6736(20)30925-9.

Getachew, B., Aubee, J.I., Schottenfeld, R.S., Csoka, A.B., Thompson, K.M., Tizabi, Y., 2018. Ketamine interactions with gut-microbiota in rats: relevance to its antidepressant and anti-inflammatory properties. BMC Microbiol 18 (1), 222. https://doi.org/10.1186/s12866-018-1373-7.

Ghosh, R., Mitra, P., Kumar, P., Goyal, T., Sharma, P., 2022. T helper cells in depression: central role of Th17 cells. Crit. Rev. Clin. Lab. Sci. 59 (1), 19–39. https://doi.org/10.1080/10408363.2021.1965535.

Gibson, G.R., Hutkins, R., Sanders, M.E., Prescott, S.L., Reimer, R.A., Salminen, S.J., Scott, K., Stanton, C., Swanson, K.S., Cani, P.D., et al., 2017. Expert consensus document: the international scientific association for probiotics and prebiotics (ISAPP) consensus statement on the definition and scope of prebiotics. Nat. Rev. Gastroenterol. Hepatol. 14 (8), 491–502. https://doi.org/10.1038/nrgastro.2017.75.

Global Health Data Exchange (GHDx), 2021. Institute of Health Metrics and Evaluation. ⟨http://ghdx.healthdata.org/gbd-results-tool?params=gbd-api-2019-permalink/d780dffbe8a381b25e1416884959e88b⟩ (Accessed 1 May 2021).

Green, J.E., Berk, M., Loughman, A., Marx, W., Castle, D., McGuinness, A.J., Cryan, J.F., Nierenberg, A.A., Athan, E., Hair, C., et al., 2021. FMT for psychiatric disorders: Following the brown brick road into the future. Bipolar Disord. 23 (7), 651–655. https://doi.org/10.1111/bdi.13124.

Grosse, L., Hoogenboezem, T., Ambree, O., Bellingrath, S., Jorgens, S., de Wit, H.J., Wijkhuijs, A.M., Arolt, V., Drexhage, H.A., 2016. Deficiencies of the T and natural killer cell system in major depressive disorder: T regulatory cell defects are associated with inflammatory monocyte activation. Brain Behav. Immun. 54, 38–44. https://doi.org/10.1016/j.bbi.2015.12.003.

Harmer, C.J., Duman, R.S., Cowen, P.J., 2017. How do antidepressants work? New perspectives for refining future treatment approaches. Lancet Psychiatry 4 (5), 409–418. https://doi.org/10.1016/S2215-0366(17)30015-9.

Hashimoto, K., 2015a. Inflammatory biomarkers as differential predictors of antidepressant response. Int. J. Mol. Med. 16 (4), 7796–7801. https://doi.org/10.3390/ijms16047796.

Hashimoto, K., 2015b. Targeting of α7 nicotinic acetylcholine receptors in the treatment of schizophrenia and the use of auditory sensory gating as a translational biomarker. Curr. Pharm. Des. 21 (26), 3797–3806. https://doi.org/10.2174/1381612821666150605111345.

Hashimoto, K., 2019. Rapid-acting antidepressant ketamine, its metabolites and other candidates: a historical overview and future perspective. Psychiatry Clin. Neurosci. 73 (10), 613–627. https://doi.org/10.1111/pcn.12902.

Hashimoto, K., 2020. Molecular mechanisms of the rapid-acting and long-lasting antidepressant actions of (*R*)-ketamine. Biochem. Pharmacol. 177, 113935 https://doi.org/10.1016/j.bcp.2020.113935.

Hashimoto, K., Fukushima, T., Shimizu, E., Komatsu, N., Watanabe, H., Shinoda, N., Nakazato, M., Kumakiri, C., Okada, S., Hasegawa, H., Imai, K., Iyo, M., 2003. Decreased serum levels of D-serine in patients with schizophrenia: evidence in support of the *N*-methyl-D-aspartate receptor hypofunction hypothesis of schizophrenia. Arch. Gen. Psychiatry 60 (6), 572–576. https://doi.org/10.1001/archpsyc.60.6.572.

Hashimoto, K., Fukushima, T., Shimizu, E., Okada, S., Komatsu, N., Okamura, N., Koike, K., Koizumi, H., Kumakiri, C., Imai, K., Iyo, M., 2004. Possible role of D-serine in the pathophysiology of Alzheimer's disease. Prog. Neuropsychopharmacol. Biol. Psychiatry 28 (2), 385–388. https://doi.org/10.1016/j.pnpbp.2003.11.009.

Hashimoto, K., Engberg, G., Shimizu, E., Nordin, C., Lindström, L.H., Iyo, M., 2005. Reduced D-serine to total serine ratio in the cerebrospinal fluid of drug naïve schizophrenic patients. Prog. Neuropsychopharmacol. Biol. Psychiatry 29 (5), 767–769. https://doi.org/10.1016/j.pnpbp.2005.04.023.

Hashimoto, K., Yoshida, T., Ishikawa, M., Fujita, Y., Niitsu, T., Nakazato, M., Watanabe, H., Sasaki, T., Shiina, A., Hashimoto, T., Kanahara, N., Hasegawa, T., Enohara, M., Kimura, A., Iyo, M., 2016. Increased serum levels of serine enantiomers in patients with depression. Acta Neuropsychiatr. 28 (3), 173–178. https://doi.org/10.1017/neu.2015.59.

Heifets, B.D., Bentzley, B.S., Williams, N., Schatzberg, A.F., 2021. Unraveling the opioid actions of *S*-ketamine and *R*-ketamine: comment on Bonaventura et al. Mol. Psychiatry 26 (11), 6104–6106. https://doi.org/10.1038/s41380-021-01167-1.

Herzog, H., 2020. Integrated pathways that control stress and energy homeostasis. Nat. Rev. Endocrinol. 16 (2), 75–76. https://doi.org/10.1038/s41574-019-0298-z.

Hinton, R., 2020. A case report looking at the effects of faecal microbiota transplantation in a patient with bipolar disorder. Aust. N. Z. J. Psychiatry 54 (6), 649–650. https://doi.org/10.1177/0004867420912834.

Hong, M., Zheng, J., Ding, Z.Y., Chen, J.H., Yu, L., Niu, Y., Hua, Y.Q., Wang, L.L., 2013. Imbalance between Th17 and Treg cells may play an important role in the development of chronic unpredictable mild stress-induced depression in mice. Neuroimmunomodulation 20 (1), 39–50. https://doi.org/10.1159/000343100.

Hoyer, D., 2020. Targeting the 5-HT system: potential side effects. Neuropharmacology 179, 108233. https://doi.org/10.1016/j.neuropharm.2020.108233.

Hsiao, E.Y., McBride, S.W., Hsien, S., Sharon, G., Hyde, E.R., McCue, T., Codelli, J.A., Chow, J., Reisman, S.E., Petrosino, J.F., et al., 2013. Microbiota modulate behavioral and physiological abnormalities associated with neurodevelopmental disorders. Cell 155 (7), 1451–1463. https://doi.org/10.1016/j.cell.2013.11.024.

Huang, N., Hua, D., Zhan, G., Li, S., Zhu, B., Jiang, R., Yang, L., Bi, J., Xu, H., Hashimoto, K., et al., 2019. Role of actinobacteria and coriobacteriia in the antidepressant effects of ketamine in an inflammation model of depression. Pharmacol. Biochem. Behav. 176, 93–100. https://doi.org/10.1016/j.pbb.2018.12.001.

Jiang, H., Ling, Z., Zhang, Y., Mao, H., Ma, Z., Yin, Y., Wang, W., Tang, W., Tan, Z., Shi, J., et al., 2015. Altered fecal microbiota composition in patients with major depressive disorder. Brain Behav. Immun. 48, 186–194. https://doi.org/10.1016/j.bbi.2015.03.016.

Kelly, J.R., Borre, Y., C, O.B., Patterson, E., El Aidy, S., Deane, J., Kennedy, P.J., Beers, S., Scott, K., Moloney, G., et al., 2016. Transferring the blues: depression-associated gut microbiota induces neurobehavioural changes in the rat. J. Psychiatr. Res. 82, 109–118. https://doi.org/10.1016/j.jpsychires.2016.07.019.

Kiecolt-Glaser, J.K., Wilson, S.J., Bailey, M.L., Andridge, R., Peng, J., Jaremka, L.M., Fagundes, C.P., Malarkey, W.B., Laskowski, B., Belury, M.A., 2018. Marital distress, depression, and a leaky gut: translocation of bacterial endotoxin as a pathway to inflammation. Psychoneuroendocrinology 98, 52–60. https://doi.org/10.1016/j.psyneuen.2018.08.007.

Kim, J., Suh, Y.H., Chang, K.A., 2021. Interleukin-17 induced by cumulative mild stress promoted depression-like behaviors in young adult mice. Mol. Brain 14 (1), 11. https://doi.org/10.1186/s13041-020-00726-x.

Klunemann, M., Andrejev, S., Blasche, S., Mateus, A., Phapale, P., Devendran, S., Vappiani, J., Simon, B., Scott, T.A., Kafkia, E., et al., 2021. Bioaccumulation of therapeutic drugs by human gut bacteria. Nature 597 (7877), 533–538. https://doi.org/10.1038/s41586-021-03891-8.

Knudsen, J.K., Michaelsen, T.Y., Bundgaard-Nielsen, C., Nielsen, R.E., Hjerrild, S., Leutscher, P., Wegener, G., Sorensen, S., 2021. Faecal microbiota transplantation from patients with depression or healthy individuals into rats modulates mood-related behaviour. Sci. Rep. 11 (1), 21869. https://doi.org/10.1038/s41598-021-01248-9.

Koh, A., Backhed, F., 2020. From association to causality: the role of the gut microbiota and its functional products on host metabolism. Mol. Cell 78 (4), 584–596. https://doi.org/10.1016/j.molcel.2020.03.005.

Lach, G., Schellekens, H., Dinan, T.G., Cryan, J.F., 2018. Anxiety, depression, and the microbiome: a role for gut peptides. Neurotherapeutics 15 (1), 36–59. https://doi.org/10.1007/s13311-017-0585-0.

Lassale, C., Batty, G.D., Baghdadli, A., Jacka, F., Sanchez-Villegas, A., Kivimaki, M., Akbaraly, T., 2019. Healthy dietary indices and risk of depressive outcomes: a systematic review and meta-analysis of observational studies. Mol. Psychiatry 24 (7), 965–986. https://doi.org/10.1038/s41380-018-0237-8.

Leal, G.C., Bandeira, I.D., Correia-Melo, F.S., Telles, M., Mello, R.P., Vieira, F., Lima, C.S., Jesus-Nunes, A.P., Guerreiro-Costa, L.N.F., Marback, R.F., et al., 2021. Intravenous arketamine for treatment-resistant depression: open-label pilot study. Eur. Arch. Psychiatry Clin. Neurosci. 271 (3), 577–582. https://doi.org/10.1007/s00406-020-01110-5.

Li, H., Xiang, Y., Zhu, Z., Wang, W., Jiang, Z., Zhao, M., Cheng, S., Pan, F., Liu, D., Ho, R. C.M., et al., 2021. Rifaximin-mediated gut microbiota regulation modulates the function of microglia and protects against CUMS-induced depression-like behaviors in adolescent rat. J. Neuroinflamm. 18 (1), 254. https://doi.org/10.1186/s12974-021-02303-y.

Li, J., Jia, X., Wang, C., Wu, C., Qin, X., 2019a. Altered gut metabolome contributes to depression-like behaviors in rats exposed to chronic unpredictable mild stress. Transl. Psychiatry 9 (1), 40. https://doi.org/10.1038/s41398-019-0391-z.

Li, J.M., Yu, R., Zhang, L.P., Wen, S.Y., Wang, S.J., Zhang, X.Y., Xu, Q., Kong, L.D., 2019b. Dietary fructose-induced gut dysbiosis promotes mouse hippocampal

neuroinflammation: a benefit of short-chain fatty acids. Microbiome 7 (1), 98. https://doi.org/10.1186/s40168-019-0713-7.

Li, N., Wang, Q., Wang, Y., Sun, A., Lin, Y., Jin, Y., Li, X., 2019c. Fecal microbiota transplantation from chronic unpredictable mild stress mice donors affects anxiety-like and depression-like behavior in recipient mice via the gut microbiota-inflammation-brain axis. Stress 22 (5), 592–602. https://doi.org/10.1080/10253890.2019.1617267.

Li, Y., Xiao, B., Qiu, W., Yang, L., Hu, B., Tian, X., Yang, H., 2010. Altered expression of CD4(+)CD25(+) regulatory T cells and its 5-HT$_{1a}$ receptor in patients with major depression disorder. J. Affect. Disord. 124 (1–2), 68–75. https://doi.org/10.1016/j.jad.2009.10.018.

Liu, R.T., Walsh, R.F.L., Sheehan, A.E., 2019. Prebiotics and probiotics for depression and anxiety: a systematic review and meta-analysis of controlled clinical trials. Neurosci. Biobehav. Rev. 102, 13–23. https://doi.org/10.1016/j.neubiorev.2019.03.023.

Liu, R.T., Rowan-Nash, A.D., Sheehan, A.E., Walsh, R.F.L., Sanzari, C.M., Korry, B.J., Belenky, P., 2020. Reductions in anti-inflammatory gut bacteria are associated with depression in a sample of young adults. Brain Behav. Immun. 88, 308–324. https://doi.org/10.1016/j.bbi.2020.03.026.

Liu, Y., Forsythe, P., 2021. Vagotomy and insights into the microbiota-gut-brain axis. Neurosci. Res. 168, 20–27. https://doi.org/10.1016/j.neures.2021.04.001.

Liu, Y., Wang, H., Gui, S., Zeng, B., Pu, J., Zheng, P., Zeng, L., Luo, Y., Wu, Y., Zhou, C., et al., 2021. Proteomics analysis of the gut-brain axis in a gut microbiota-dysbiosis model of depression. Transl. Psychiatry 11 (1), 568. https://doi.org/10.1038/s41398-021-01689-w.

Long-Smith, C., O'Riordan, K.J., Clarke, G., Stanton, C., Dinan, T.G., Cryan, J.F., 2020. Microbiota-gut-brain axis: new therapeutic opportunities. Annu. Rev. Pharmacol. Toxicol. 60, 477–502. https://doi.org/10.1146/annurev-pharmtox-010919-023628.

Lourenco, C., Kelly, D., Cantillon, J., Cauchi, M., Yon, M.A., Bentley, L., Cox, R.D., Turner, C., 2019. Monitoring type 2 diabetes from volatile faecal metabolome in Cushing's syndrome and single Afmid mouse models via a longitudinal study. Sci. Rep. 9 (1), 18779. https://doi.org/10.1038/s41598-019-55339-9.

Lukic, I., Getselter, D., Ziv, O., Oron, O., Reuveni, E., Koren, O., Elliott, E., 2019. Antidepressants affect gut microbiota and *Ruminococcus flavefaciens* is able to abolish their effects on depressive-like behavior. Transl. Psychiatry 9 (1), 133. https://doi.org/10.1038/s41398-019-0466-x.

Lynch, S.V., Pedersen, O., 2016. The human intestinal microbiome in health and disease. New Engl. J. Med. 375 (24), 2369–2379. https://doi.org/10.1056/NEJMra1600266.

Macedo, D., Filho, A., Soares de Sousa, C.N., Quevedo, J., Barichello, T., Junior, H.V.N., Freitas de Lucena, D., 2017. Antidepressants, antimicrobials or both? Gut microbiota dysbiosis in depression and possible implications of the antimicrobial effects of antidepressant drugs for antidepressant effectiveness. J. Affect. Disord. 208, 22–32. https://doi.org/10.1016/j.jad.2016.09.012.

Maehata, H., Kobayashi, Y., Mitsuyama, E., Kawase, T., Kuhara, T., Xiao, J.Z., Tsukahara, T., Toyoda, A., 2019. Heat-killed *Lactobacillus helveticus* strain MCC1848 confers resilience to anxiety or depression-like symptoms caused by subchronic social defeat stress in mice. Biosci. Biotechnol. Biochem. 83 (7), 1239–1247. https://doi.org/10.1080/09168451.2019.1591263.

Maiuolo, J., Gliozzi, M., Musolino, V., Carresi, C., Scarano, F., Nucera, S., Scicchitano, M., Oppedisano, F., Bosco, F., Ruga, S., et al., 2021. The contribution of gut microbiota-brain axis in the development of brain disorders. Front. Neurosci. 15, 616883 https://doi.org/10.3389/fnins.2021.616883.

Marcondes Avila, P.R., Fiorot, M., Michels, M., Dominguini, D., Abatti, M., Vieira, A., de Moura, A.B., Behenck, J.P., Borba, L.A., Botelho, M.E.M., et al., 2020. Effects of microbiota transplantation and the role of the vagus nerve in gut-brain axis in animals subjected to chronic mild stress. J. Affect. Disord. 277, 410–416. https://doi.org/10.1016/j.jad.2020.08.013.

Margolis, K.G., Cryan, J.F., Mayer, E.A., 2021. The microbiota-gut-brain axis: from motility to mood. Gastroenterology 160 (5), 1486–1501. https://doi.org/10.1053/j.gastro.2020.10.066.

Martin, C.R., Osadchiy, V., Kalani, A., Mayer, E.A., 2018. The brain-gut-microbiome axis. Cell Mol. Gastroenterol. Hepatol. 6 (2), 133–148. https://doi.org/10.1016/j.jcmgh.2018.04.003.

Marx, W., Hoare, E., Jacka, F., 2019. Chapter 25 - diet and depression: from epidemiology to novel therapeutics. In: Quevedo, J., Carvalho, A.F., Zarate, C.A. (Eds.), Neurobiology of Depression. Academic Press, pp. 285–292. https://doi.org/10.1016/B978-0-12-813333-0.00025-1.

Marx, W., Lane, M., Hockey, M., Aslam, H., Berk, M., Walder, K., Borsini, A., Firth, J., Pariante, C.M., Berding, K., et al., 2021. Exploring the biological mechanisms of action. Mol. Psychiatry 26 (1), 134–150. https://doi.org/10.1038/s41380-020-00925-x.

Matsumoto, M., Kunisawa, A., Hattori, T., Kawana, S., Kitada, Y., Tamada, H., Kawano, S., Hayakawa, Y., Iida, J., Fukusaki, E., 2018. Free D-amino acids produced by commensal bacteria in the colonic lumen. Sci. Rep. 8 (1), 17915. https://doi.org/10.1038/s41598-018-36244-z.

McGovern, A.S., Hamlin, A.S., Winter, G., 2019. A review of the antimicrobial side of antidepressants and its putative implications on the gut microbiome. Aust. N.Z. J. Psychiatry 53 (12), 1151–1166. https://doi.org/10.1177/0004867419877954.

McVey Neufeld, K.A., Bienenstock, J., Bharwani, A., Champagne-Jorgensen, K., Mao, Y., West, C., Liu, Y., Surette, M.G., Kunze, W., Forsythe, P., 2019. Oral selective serotonin reuptake inhibitors activate vagus nerve dependent gut-brain signalling. Sci. Rep. 9 (1), 14290. https://doi.org/10.1038/s41598-019-50807-8.

Medina-Rodriguez, E.M., Madorma, D., O'Connor, G., Mason, B.L., Han, D., Deo, S.K., Oppenheimer, M., Nemeroff, C.B., Trivedi, M.H., Daunert, S., et al., 2020. Identification of a signaling mechanism by which the microbiome regulates Th17 cell-mediated depressive-like behaviors in mice. Am. J. Psychiatry 177 (10), 974–990. https://doi.org/10.1176/appi.ajp.2020.19090960.

Merchak, A., Gaultier, A., 2020. Microbial metabolites and immune regulation: new targets for major depressive disorder. Brain Behav. Immun. Health 9, 100169. https://doi.org/10.1016/j.bbih.2020.100169.

Merrick, B., Allen, L., Masirah, M., Zain, N., Forbes, B., Shawcross, D.L., Goldenberg, S. D., 2020. Regulation, risk and safety of faecal microbiota transplant. Infect. Prev. Pract. 2 (3), 100069 https://doi.org/10.1016/j.infpip.2020.100069.

Milani, C., Duranti, S., Bottacini, F., Casey, E., Turroni, F., Mahony, J., Belzer, C., Delgado Palacio, S., Arboleya Montes, S., Mancabelli, L., et al., 2017. The first microbial colonizers of the human gut: composition, activities, and health implications of the infant gut microbiota. Microbiol. Mol. Biol. Rev. 81 (4), e00036–17. https://doi.org/10.1128/MMBR.00036-17.

Misra, S., Mohanty, D., 2019. Psychobiotics: a new approach for treating mental illness? Crit. Rev. Food Sci. Nutr. 59 (8), 1230–1236. https://doi.org/10.1080/10408398.2017.1399860.

Morais, L.H., Schreiber, H.Lt, Mazmanian, S.K., 2021. The gut microbiota-brain axis in behaviour and brain disorders. Nat. Rev. Microbiol. 19 (4), 241–255. https://doi.org/10.1038/s41579-020-00460-0.

Nakade, Y., Iwata, Y., Furuichi, K., Mita, M., Hamase, K., Konno, R., Miyake, T., Sakai, N., Kitajima, S., Toyama, T., et al., 2018. Gut microbiota-derived D-serine protects against acute kidney injury. JCI Insight 3 (20), e97957. https://doi.org/10.1172/jci.insight.97957.

Naseribafrouei, A., Hestad, K., Avershina, E., Sekelja, M., Linlokken, A., Wilson, R., Rudi, K., 2014. Correlation between the human fecal microbiota and depression. Neurogastroenterol. Motil. 26 (8), 1155–1162. https://doi.org/10.1111/nmo.12378.

Niesler, B., Kuerten, S., Demir, I.E., Schafer, K.H., 2021. Disorders of the enteric nervous system - a holistic view. Nat. Rev. Gastroenterol. Hepatol. 18 (6), 393–410. https://doi.org/10.1038/s41575-020-00385-2.

Nikolova, V.L., Hall, M.R.B., Hall, L.J., Cleare, A.J., Stone, J.M., Young, A.H., 2021. Pertubations in gut microbiota composition in psychiatric disorders: a review and meta-analysis. JAMA Psychiatry 78 (12), 1343–1354. https://doi.org/10.1001/jamapsychiatry.2021.2573.

Nishi, D., Su, K.P., Usuda, K., Chang, J.P., Hamazaki, K., Ishima, T., Sano, Y., Ito, H., Isaka, K., Tachibana, Y., Tanigaki, S., Suzuki, T., Hashimoto, K., Matsuoka, Y.J., 2020. Plasma estradil levels and antidepressant effects of omega-3 fatty acids in pregnant women. Brain Behav. Immun. 85, 29–34. https://doi.org/10.1016/j.bbi.2019.02.014.

Noble, E.E., Hsu, T.M., Kanoski, S.E., 2017. Gut to brain dysbiosis: mechanisms linking western diet consumption, the microbiome, and cognitive Impairment. Front. Behav. Neurosci. 11, 9. https://doi.org/10.3389/fnbeh.2017.00009.

O'Hara, A.M., Shanahan, F., 2006. The gut flora as a forgotten organ. EMBO Rep. 7 (7), 688–693. https://doi.org/10.1038/sj.embor.7400731.

Okubo, R., Matsuoka, Y.J., Sawada, N., Mimura, M., Kurotani, K., Nozaki, S., Shikimoto, R., Tsugane, S., 2019. Diet quality and depression risk in a Japanese population: the Japan Public Health Center (JPHC)-based prospective study. Sci. Rep. 9 (1), 7150. https://doi.org/10.1038/s41598-019-43085-x.

Opie, R.S., Itsiopoulos, C., Parletta, N., Sanchez-Villegas, A., Akbaraly, T.N., Ruusunen, A., Jacka, F.N., 2017. Dietary recommendations for the prevention of depression. Nutr. Neurosci. 20 (3), 161–171. https://doi.org/10.1179/1476830515Y.0000000043.

Osborne, L.M., Brar, A., Klein, S.L., 2019. The role of Th17 cells in the pathophysiology of pregnancy and perinatal mood and anxiety disorders. Brain Behav. Immun. 76, 7–16. https://doi.org/10.1016/j.bbi.2018.11.015.

Pandiyan, P., Bhaskaran, N., Zou, M., Schneider, E., Jayaraman, S., Huehn, J., 2019. Microbiome dependent regulation of Tregs and Th17 Cells in mucosa. Front. Immunol. 10, 426. https://doi.org/10.3389/fimmu.2019.00426.

Park, A.J., Collins, J., Blennerhassett, P.A., Ghia, J.E., Verdu, E.F., Bercik, P., Collins, S. M., 2013. Altered colonic function and microbiota profile in a mouse model of chronic depression. Neurogastroenterol. Motil. 25 (9), 733–e575. https://doi.org/10.1111/nmo.12153.

Parker, A., Fonseca, S., Carding, S.R., 2020. Gut microbes and metabolites as modulators of blood-brain barrier integrity and brain health. Gut Microbes 11 (2), 135–157. https://doi.org/10.1080/19490976.2019.1638722.

Pavlov, V.A., Tracey, K.J., 2012. The vagus nerve and the inflammatory reflex–linking immunity and metabolism. Nat. Rev. Endocrinol. 8 (12), 743–754. https://doi.org/10.1038/nrendo.2012.189.

Poletti, S., de Wit, H., Mazza, E., Wijkhuijs, A.J.M., Locatelli, C., Aggio, V., Colombo, C., Benedetti, F., Drexhage, H.A., 2017. Th17 cells correlate positively to the structural and functional integrity of the brain in bipolar depression and healthy controls. Brain Behav. Immun. 61, 317–325. https://doi.org/10.1016/j.bbi.2016.12.020.

Psaltopoulou, T., Sergentanis, T.N., Panagiotakos, D.B., Sergentanis, I.N., Kosti, R., Scarmeas, N., 2013. Mediterranean diet, stroke, cognitive impairment, and depression: a meta-analysis. Ann. Neurol. 74 (4), 580–591. https://doi.org/10.1002/ana.23944.

Pu, Y., Tan, Y., Qu, Y., Chang, L., Wang, S., Wei, Y., Wang, X., Hashimoto, K., 2021. A role of the subdiaphragmatic vagus nerve in depression-like phenotypes in mice after fecal microbiota transplantation from *Chrna7* knock-out mice with depression-like phenotypes. Brain Behav. Immun. 94, 318–326. https://doi.org/10.1016/j.bbi.2020.12.032.

Qu, Y., Yang, C., Ren, Q., Ma, M., Dong, C., Hashimoto, K., 2017. Comparison of (*R*)-ketamine and lanicemine on depression-like phenotype and abnormal composition of gut microbiota in a social defeat stress model. Sci. Rep. 7 (1), 15725. https://doi.org/10.1038/s41598-017-16060-7.

Qu, Y., Zhang, K., Pu, Y., Chang, L., Wang, S., Tan, Y., Wang, X., Zhang, J., Ohnishi, T., Yoshikawa, T., Hashimoto, K., 2020. Betaine supplementation is associated with the

resilience in mice after chronic social defeat stress: a role of brain-gut-microbiota axis. J. Affect. Disord. 272, 66–76. https://doi.org/10.1016/j.jad.2020.03.095.

Ramsteijn, A.S., Jasarevic, E., Houwing, D.J., Bale, T.L., Olivier, J.D., 2020. Antidepressant treatment with fluoxetine during pregnancy and lactation modulates the gut microbiome and metabolome in a rat model relevant to depression. Gut Microbes 11 (4), 735–753. https://doi.org/10.1080/19490976.2019.1705728.

Rao, J., Qiao, Y., Xie, R., Lin, L., Jiang, J., Wang, C., Li, G., 2021a. Fecal microbiota transplantation ameliorates stress-induced depression-like behaviors associated with the inhibition of glial and NLRP3 inflammasome in rat brain. J. Psychiatr. Res. 137, 147–157. https://doi.org/10.1016/j.jpsychires.2021.02.057.

Rao, J., Xie, R., Lin, L., Jiang, J., Du, L., Zeng, X., Li, G., Wang, C., Qiao, Y., 2021b. Fecal microbiota transplantation ameliorates gut microbiota imbalance and intestinal barrier damage in rats with stress-induced depressive-like behavior. Eur. J. Neurosci. 53 (11), 3598–3611. https://doi.org/10.1111/ejn.15192.

Rosas-Ballina, M., Tracey, K.J., 2009. The neurology of the immune system: neural reflexes regulate immunity. Neuron 64 (1), 28–32. https://doi.org/10.1016/j.neuron.2009.09.039.

Rowland, I., Gibson, G., Heinken, A., Scott, K., Swann, J., Thiele, I., Tuohy, K., 2018. Gut microbiota functions: metabolism of nutrients and other food components. Eur. J. Nutr. 57 (1), 1–24. https://doi.org/10.1007/s00394-017-1445-8.

Rudzki, L., Maes, M., 2020. The microbiota-gut-immune-Glia (MGIG) Axis in major depression. Mol. Neurobiol. 57 (10), 4269–4295. https://doi.org/10.1007/s12035-020-01961-y.

Salvo-Romero, E., Stokes, P., Gareau, M.G., 2020. Microbiota-immune interactions: from gut to brain. LymphoSign J. 7 (1), 1–23. https://doi.org/10.14785/lymphosign-2019-0018.

Sanada, K., Nakajima, S., Kurokawa, S., Barceló-Soler, A., Ikuse, D., Hirata, A., Yoshizawa, A., Tomizawa, Y., Salas-Valero, M., Noda, Y., et al., 2020. Gut microbiota and major depressive disorder: a systematic review and meta-analysis. J. Affect. Disord. 266, 1–13. https://doi.org/10.1016/j.jad.2020.01.102.

Sarkar, A., Lehto, S.M., Harty, S., Dinan, T.G., Cryan, J.F., Burnet, P.W.J., 2016. Psychobiotics and the manipulation of bacteria-gut-brain signals. Trends Neurosci. 39 (11), 763–781. https://doi.org/10.1016/j.tins.2016.09.002.

Sasabe, J., Suzuki, M., 2018. Emerging role of D-amino acid metabolism in the innate defense. Front. Microbiol. 9, 933. https://doi.org/10.3389/fmicb.2018.00933.

Schiweck, C., Valles-Colomer, M., Arolt, V., Muller, N., Raes, J., Wijkhuijs, A., Claes, S., Drexhage, H., Vrieze, E., 2020. Depression and suicidality: a link to premature T helper cell aging and increased Th17 cells. Brain Behav. Immun. 87, 603–609. https://doi.org/10.1016/j.bbi.2020.02.005.

Schmidtner, A.K., Slattery, D.A., Glasner, J., Hiergeist, A., Gryksa, K., Malik, V.A., Hellmann-Regen, J., Heuser, I., Baghai, T.C., Gessner, A., et al., 2019. Minocycline alters behavior, microglia and the gut microbiome in a trait-anxiety-dependent manner. Transl. Psychiatry 9 (1), 223. https://doi.org/10.1038/s41398-019-0556-9.

Seki, D., Mayer, M., Hausmann, B., Pjevac, P., Giordano, V., Goeral, K., Unterasinger, L., Klebermaß-Schrehof, K., De Paepe, K., Van de Wiele, T., et al., 2021. Aberrant gut-microbiota-immune-brain axis development in premature neonates with brain damage. Cell Host Microbe 29 (10), 1558–1572. https://doi.org/10.1016/j.chom.2021.08.004.

Sender, R., Fuchs, S., Milo, R., 2016. Are we really vastly outnumbered? Revisiting the ratio of bacterial to host. Cells Hum. Cell 164 (3), 337–340. https://doi.org/10.1016/j.cell.2016.01.013.

Settanni, C.R., Ianiro, G., Bibbo, S., Cammarota, G., Gasbarrini, A., 2021. Gut microbiota alteration and modulation in psychiatric disorders: current evidence on fecal microbiota transplantation. Prog. Neuropsychopharmacol. Biol. Psychiatry 109, 110258. https://doi.org/10.1016/j.pnpbp.2021.110258.

Sharma, S., Zhuang, Y., Gomez-Pinilla, F., 2012. Diet transition to a high-fat diet for 3 weeks reduces brain omega-3-fatty acid levels, alters BDNF signaling and induces anxiety & depression-like behavior in adult rats. Nat. Preced. https://doi.org/10.1038/npre.2012.6950.1.

Shen, Y., Yang, X., Li, G., Gao, J., Liang, Y., 2021. The change of gut microbiota in MDD patients under SSRIs treatment. Sci. Rep. 11 (1), 14918. https://doi.org/10.1038/s41598-021-94481-1.

Silva, Y.P., Bernardi, A., Frozza, R.L., 2020. The role of short-chain fatty acids from gut microbiota in gut-brain communication. Front. Endocrinol. 11, 25. https://doi.org/10.3389/fendo.2020.00025.

Simpson, C.A., Diaz-Arteche, C., Eliby, D., Schwartz, O.S., Simmons, J.G., Cowan, C.S.M., 2021. The gut microbiota in anxiety and depression - a systematic review. Clin. Psychol. Rev. 83, 101943 https://doi.org/10.1016/j.cpr.2020.101943.

Siopi, E., Chevalier, G., Katsimpardi, L., Saha, S., Bigot, M., Moigneu, C., Eberl, G., Lledo, P.M., 2020. Changes in gut microbiota by chronic stress impair the efficacy of fluoxetine. Cell Rep. 30 (11), 3682–3690. https://doi.org/10.1016/j.celrep.2020.02.099.

Smith, K.S., Greene, M.W., Babu, J.R., Fruge, A.D., 2021. Psychobiotics as treatment for anxiety, depression, and related symptoms: a systematic review. Nutr. Neurosci. 24 (12), 963–977. https://doi.org/10.1080/1028415X.2019.1701220.

Stevens, B.R., Roesch, L., Thiago, P., Russell, J.T., Pepine, C.J., Holbert, R.C., Raizada, M. K., Triplett, E.W., 2021. Depression phenotype identified by using single nucleotide exact amplicon sequence variants of the human gut microbiome. Mol. Psychiatry 26, 4277–4287. https://doi.org/10.1038/s41380-020-0652-5.

Stilling, R.M., van de Wouw, M., Clarke, G., Stanton, C., Dinan, T.G., Cryan, J.F., 2016. The neuropharmacology of butyrate: The bread and butter of the microbiota-gut-brain axis? Neurochem. Int. 99, 110–132. https://doi.org/10.1016/j.neuint.2016.06.011.

Sudo, N., Chida, Y., Aiba, Y., Sonoda, J., Oyama, N., Yu, X.N., Kubo, C., Koga, Y., 2004. Postnatal microbial colonization programs the hypothalamic-pituitary-adrenal system for stress response in mice. J. Physiol. 558 (Pt 1), 263–275. https://doi.org/10.1113/jphysiol.2004.063388.

Sun, L., Zhang, H., Cao, Y., Wang, C., Zhao, C., Wang, H., Cui, G., Wang, M., Pan, Y., Shi, Y., et al., 2019. Fluoxetine ameliorates dysbiosis in a depression model induced by chronic unpredicted mild stress in mice. Int. J. Med. Sci. 16 (9), 1260–1270. https://doi.org/10.7150/ijms.37322.

Sun, T., Nguyen, A., Gommerman, J.L., 2020a. Dendritic cell subsets in intestinal immunity and inflammation. J. Immunol. 204 (5), 1075–1083. https://doi.org/10.4049/jimmunol.1900710.

Sun, Y., Yan, T., Gong, G., Li, Y., Zhang, J., Wu, B., Bi, K., Jia, Y., 2020b. Antidepressant-like effects of Schisandrin on lipopolysaccharide-induced mice: gut microbiota, short chain fatty acid and TLR4/NF-kappaB signaling pathway. Int. Immunopharmacol. 89 (Pt A), 107029 https://doi.org/10.1016/j.intimp.2020.107029.

Tao, J., Campbell, J.N., Tsai, L.T., Wu, C., Liberles, S.D., Lowell, B.B., 2021. Highly selective brain-to-gut communication via genetically defined vagus neurons. Neuron 109 (13), 2106–2115. https://doi.org/10.1016/j.neuron.2021.05.004.

Thursby, E., Juge, N., 2017. Introduction to the human gut microbiota. Biochem J. 474 (11), 1823–1836. https://doi.org/10.1042/BCJ20160510.

Tian, P., O'Riordan, K.J., Lee, Y.K., Wang, G., Zhao, J., Zhang, H., Cryan, J.F., Chen, W., 2020. Towards a psychobiotic therapy for depression: bifidobacterium breve CCFM1025 reverses chronic stress-induced depressive symptoms and gut microbial abnormalities in mice. Neurobiol. Stress 12, 100216. https://doi.org/10.1016/j.ynstr.2020.100216.

Tillmann, S., Abildgaard, A., Winther, G., Wegener, G., 2019. Altered fecal microbiota composition in the flinders sensitive line rat model of depression. Psychopharmacology 236 (5), 1445–1457. https://doi.org/10.1007/s00213-018-5094-2.

Track, N.S., 1980. The gastrointestinal endocrine system. Can. Med. Assoc. J. 122 (3), 287–292.

Vagena, E., Ryu, J.K., Baeza-Raja, B., Walsh, N.M., Syme, C., Day, J.P., Houslay, M.D., Baillie, G.S., 2019. A high-fat diet promotes depression-like behavior in mice by suppressing hypothalamic PKA signaling. Transl. Psychiatry 9 (1), 141. https://doi.org/10.1038/s41398-019-0470-1.

Vaghef-Mehrabany, E., Maleki, V., Behrooz, M., Ranjbar, F., Ebrahimi-Mameghani, M., 2020. Can psychobiotics "mood" ify gut? An update systematic review of randomized controlled trials in healthy and clinical subjects, on anti-depressant effects of probiotics, prebiotics, and synbiotics. Clin. Nutr. 39 (5), 1395–1410. https://doi.org/10.1016/j.clnu.2019.06.004.

Valles-Colomer, M., Falony, G., Darzi, Y., Tigchelaar, E.F., Wang, J., Tito, R.Y., Schiweck, C., Kurilshikov, A., Joossens, M., Wijmenga, C., et al., 2019. The neuroactive potential of the human gut microbiota in quality of life and depression. Nat. Microbiol. 4 (4), 623–632. https://doi.org/10.1038/s41564-018-0337-x.

van de Wouw, M., Boehme, M., Lyte, J.M., Wiley, N., Strain, C., O'Sullivan, O., Clarke, G., Stanton, C., Dinan, T.G., Cryan, J.F., 2018. Short-chain fatty acids: Microbial metabolites that alleviate stress-induced brain-gut axis alterations. J. Physiol. 596 (20), 4923–4944. https://doi.org/10.1113/JP276431.

van der Hee, B., Wells, J.M., 2021. Microbial regulation of host physiology by short-chain fatty acids. Trends Microbiol. 29 (8), 700–712. https://doi.org/10.1016/j.tim.2021.02.001.

Vijay, A., Kouraki, A., Gohir, S., Turnbull, J., Kelly, A., Chapman, V., Barrett, D.A., Bulsiewicz, W.J., Valdes, A.M., 2021. The anti-inflammatory effect of bacterial short chain fatty acids is partially mediated by endocannabinoids. Gut Microbes 13 (1), 1997559. https://doi.org/10.1080/19490976.2021.1997559.

Vrieze, A., Van Nood, E., Holleman, F., Salojarvi, J., Kootte, R.S., Bartelsman, J.F., Dallinga-Thie, G.M., Ackermans, M.T., Serlie, M.J., Oozeer, R., et al., 2012. Transfer of intestinal microbiota from lean donors increases insulin sensitivity in individuals with metabolic syndrome. Gastroenterology 143 (4), 913–916. https://doi.org/10.1053/j.gastro.2012.06.031.

Vujkovic-Cvijin, I., Sklar, J., Jiang, L., Natarajan, L., Knight, R., Belkaid, Y., 2020. Host variables confound gut microbiota studies of human disease. Nature 587 (7834), 448–454. https://doi.org/10.1038/s41586-020-2881-9.

Vuong, H.E., Yano, J.M., Fung, T.C., Hsiao, E.Y., 2017. The Microbiome and host behavior. Annu. Rev. Neurosci. 40, 21–49. https://doi.org/10.1146/annurev-neuro-072116-031347.

Wang, H., Yu, M., Ochani, M., Amella, C.A., Tanovic, M., Susarla, S., Li, J.H., Wang, H., Yang, H., Ulloa, L., et al., 2003. Nicotinic acetylcholine receptor alpha7 subunit is an essential regulator of inflammation. Nature 421 (6921), 384–388. https://doi.org/10.1038/nature01339.

Wang, H., Liu, L., Rao, X., Zeng, B., Yu, Y., Zhou, C., Zeng, L., Zheng, P., Pu, J., Xu, S., et al., 2020a. Integrated phosphoproteomic and metabolomic profiling reveals perturbed pathways in the hippocampus of gut microbiota dysbiosis mice. Transl. Psychiatry 10 (1), 346. https://doi.org/10.1038/s41398-020-01024-9.

Wang, S., Ishima, T., Zhang, J., Qu, Y., Chang, L., Pu, Y., Fujita, Y., Tan, Y., Wang, X., Hashimoto, K., 2020b. Ingestion of *Lactobacillus intestinalis* and *Lactobacillus reuteri* causes depression- and anhedonia-like phenotypes in antibiotic-treated mice via the vagus nerve. J. Neuroinflamm. 17 (1), 241. https://doi.org/10.1186/s12974-020-01916-z.

Wang, S., Qu, Y., Chang, L., Pu, Y., Zhang, K., Hashimoto, K., 2020c. Antibiotic-induced microbiome depletion is associated with resilience in mice after chronic social defeat stress. J. Affect. Disord. 260, 448–457. https://doi.org/10.1016/j.jad.2019.09.064.

Wang, S., Ishima, T., Qu, Y., Shan, J., Chang, L., Wei, Y., Zhang, J., Pu, Y., Fujita, Y., Tan, Y., Wang, X., Ma, L., Wan, X., Hammock, B.D., Hashimoto, K., 2021. Ingestion of *Faecalibacterium rodentium* causes depression-like phenotypes in resilient *Ephx2* knock-out mice: a role of brain–gut–microbiota axis via the subdiaphragmatic vagus nerve. J. Affect. Disord. 292, 565–573. https://doi.org/10.1016/j.jad.2021.06.006.

Wang, Y., Xu, X., Luo, A., Yang, C., 2020d. The role of gut microbiota in the antidepressant effects of ketamine. In: Hashimoto, K., Ide, S., Ikeda, K. (Eds.), Ketamine: From Abused Drug to Rapid-acting Antidepressant. Springer Nature Publisher, pp. 127–141. https://doi.org/10.1007/978-981-15-2902-3_8 (edited by).

Wei, Y., Chang, L., Hashimoto, K., 2020. A historical review of antidepressant effects of ketamine and its enantiomers. Pharmacol. Biochem. Behav. 190, 172870 https://doi.org/10.1016/j.pbb.2020.172870.

Wei, Y., Chang, L., Hashimoto, K., 2021. Molecular mechanisms underlying the antidepressant actions of arketamine: beyond the NMDA receptor. Mol. Psychiatry. https://doi.org/10.1038/s41380-021-01121-1.

Westfall, S., Caracci, F., Estill, M., Frolinger, T., Shen, L., Pasinetti, G.M., 2021a. Chronic stress-induced depression and anxiety priming modulated by gut-brain-axis immunity. Front. Immunol. 12, 670500 https://doi.org/10.3389/fimmu.2021.670500.

Westfall, S., Caracci, F., Zhao, D., Wu, Q.L., Frolinger, T., Simon, J., Pasinetti, G.M., 2021b. Microbiota metabolites modulate the T helper 17 to regulatory T cell (Th17/Treg) imbalance promoting resilience to stress-induced anxiety- and depressive-like behaviors. Brain Behav. Immun. 91, 350–368. https://doi.org/10.1016/j.bbi.2020.10.013.

Wilkowska, A., Szalach, L.P., Cubala, W.J., 2021. Gut microbiota in depression: a focus on ketamine. Front. Behav. Neurosci. 15, 693362 https://doi.org/10.3389/fnbeh.2021.693362.

Wu, M., Tian, T., Mao, Q., Zou, T., Zhou, C.J., Xie, J., Chen, J.J., 2020. Associations between disordered gut microbiota and changes of neurotransmitters and short-chain fatty acids in depressed mice. Transl. Psychiatry 10 (1), 350. https://doi.org/10.1038/s41398-020-01038-3.

Wu, P.Y., Chen, K.M., Belcastro, F., 2021a. Dietary patterns and depression risk in older adults: systematic review and meta-analysis. Nutr. Rev. 79 (9), 976–987. https://doi.org/10.1093/nutrit/nuaa118.

Wu, W.L., Adame, M.D., Liou, C.W., Barlow, J.T., Lai, T.T., Sharon, G., Schretter, C.E., Needham, B.D., Wang, M.I., Tang, W., et al., 2021b. Microbiota regulate social behaviour via stress response neurons in the brain. Nature 595 (7867), 409–414. https://doi.org/10.1038/s41586-021-03669-y.

Xiao, S., Jiang, S., Qian, D., Duan, J., 2020. Modulation of microbially derived short-chain fatty acids on intestinal homeostasis, metabolism, and neuropsychiatric disorder. Appl. Microbiol. Biotechnol. 104 (2), 589–601. https://doi.org/10.1007/s00253-019-10312-4.

Xu, H.M., Huang, H.L., Zhou, Y.L., Zhao, H.L., Xu, J., Shou, D.W., Liu, Y.D., Zhou, Y.J., Nie, Y.Q., 2021. Fecal microbiota transplantation: a new therapeutic attempt from the gut to the brain. Gastroenterol. Res. Pract. 2021, 6699268 https://doi.org/10.1155/2021/6699268.

Yamada, K., Ohnishi, T., Hashimoto, K., Ohba, H., Iwayama-Shigeno, Y., Toyoshima, M., Okuno, A., Takao, H., Toyota, T., Minabe, Y., et al., 2005. Identification of multiple serine racemase (SRR) mRNA isoforms and genetic analyses of SRR and DAO in schizophrenia and D-serine levels. Biol. Psychiatry 57 (12), 1493–1503. https://doi.org/10.1016/j.biopsych.2005.03.018.

Yamawaki, Y., Yoshioka, N., Nozaki, K., Ito, H., Oda, K., Harada, K., Shirawachi, S., Asano, S., Aizawa, H., Yamawaki, S., et al., 2018. Sodium butyrate abolishes lipopolysaccharide-induced depression-like behaviors and hippocampal microglial activation in mice. Brain Res. 1680, 13–38. https://doi.org/10.1016/j.brainres.2017.12.004.

Yang, B., Yang, C., Ren, Q., Zhang, J.C., Chen, Q.X., Shirayama, Y., Hashimoto, K., 2016a. Regional differences in the expression of brain-derived neurotrophic factor (BDNF) pro-peptide, proBDNF and preproBDNF in the brain confer stress resilience. Eur. Arch. Psychiatry Clin. Neurosci. 266 (8), 765–769. https://doi.org/10.1007/s00406-016-0693-6.

Yang, C., Shirayama, Y., Zhang, J.C., Ren, Q., Hashimoto, K., 2015a. Regional differences in brain-derived neurotrophic factor levels and dendritic spine density confer resilience to inescapable stress. Int. J. Neuropsychopharmacol. 18 (7), pyu121. https://doi.org/10.1093/ijnp/pyu121.

Yang, C., Shirayama, Y., Zhang, J.C., Ren, Q., Hashimoto, K., 2015b. Peripheral interleukin-6 promotes resilience versus susceptibility to inescapable electric stress. Acta Neuropsychiatr. 27 (5), 312–316. https://doi.org/10.1017/neu.2015.36.

Yang, C., Shirayama, Y., Zhang, J.C., Ren, Q., Yao, W., Ma, M., Dong, C., Hashimoto, K., 2015c. R-ketamine: a rapid-onset and sustained antidepressant without psychotomimetic side effects. Transl. Psychiatry 5 (9), e632. https://doi.org/10.1038/tp.2015.136.

Yang, C., Fujita, Y., Ren, Q., Ma, M., Dong, C., Hashimoto, K., 2017a. *Bifidobacterium* in the gut microbiota confer resilience to chronic social defeat stress in mice. Sci. Rep. 7, 45942. https://doi.org/10.1038/srep45942.

Yang, C., Qu, Y., Fujita, Y., Ren, Q., Ma, M., Dong, C., Hashimoto, K., 2017b. Possible role of the gut microbiota-brain axis in the antidepressant effects of (*R*)-ketamine in a social defeat stress model. Transl. Psychiatry 7 (12), 1294. https://doi.org/10.1038/s41398-017-0031-4.

Yang, J., Zheng, P., Li, Y., Wu, J., Tan, X., Zhou, J., Sun, Z., Chen, X., Zhang, G., Zhang, H., et al., 2020a. Landscapes of bacterial and metabolic signatures and their interaction in major depressive disorders. Sci. Adv. 6 (49) https://doi.org/10.1126/sciadv.aba8555.

Yang, J.L., Liu, X., Jiang, H., Pan, F., Ho, C.S., Ho, R.C., 2016b. The effects of high-fat-diet combined with chronic unpredictable mild stress on depression-like behavior and Leptin/LepRb in male rats. Sci. Rep. 6, 35239. https://doi.org/10.1038/srep35239.

Yang, Y., Ishima, T., Wan, X., Wei, Y., Chang, L., Zhang, J., Qu, Y., Hashimoto, K., 2021. Microglial depletion and abnormalities in gut microbiota composition and short-chain fatty acids in mice after repeated administration of colony stimulating factor 1 receptor inhibitor PLX5622. Eur. Arch. Psychiatry Clin. Neurosci. 2021 (Sep 4) https://doi.org/10.1007/s00406-021-01325-0.

Yang, Z., Li, J., Gui, X., Shi, X., Bao, Z., Han, H., Li, M.D., 2020b. Updated review of research on the gut microbiota and their relation to depression in animals and human beings. Mol. Psychiatry 25 (11), 2759–2772. https://doi.org/10.1038/s41380-020-0729-1.

Yao, W., Cao, Q., Luo, S., He, L., Yang, C., Chen, J., Qi, Q., Hashimoto, K., Zhang, J.C., 2021. Microglial ERK-NRBP1-CREB-BDNF signaling in sustained antidepressant actions of (*R*)-ketamine. Mol. Psychiatry. https://doi.org/10.1038/s41380-021-01377-7.

Yirmiya, R., Rimmerman, N., Reshef, R., 2015. Depression as a microglial disease. Trends Neurosci. 38 (10), 637–658. https://doi.org/10.1016/j.tins.2015.08.001.

Yoo, B.B., Mazmanian, S.K., 2017. The Enteric network: interactions between the immune and nervous systems of the gut. Immunity 46 (6), 910–926. https://doi.org/10.1016/j.immuni.2017.05.011.

Zhang, J., Ma, L., Chang, L., Pu, Y., Qu, Y., Hashimoto, K., 2020a. A key role of the subdiaphragmatic vagus nerve in the depression-like phenotype and abnormal composition of gut microbiota in mice after lipopolysaccharide administration. Transl. Psychiatry 10 (1), 186. https://doi.org/10.1038/s41398-020-00878-3.

Zhang, J.C., Li, S.X., Hashimoto, K., 2014. *R*(-)-ketamine shows greater potency and longer lasting antidepressant effects than *S*(+)-ketamine. Pharmacol. Biochem. Behav. 116, 137–141. https://doi.org/10.1016/j.pbb.2013.11.033.

Zhang, J.C., Yao, W., Ren, Q., Yang, C., Dong, C., Ma, M., Wu, J., Hashimoto, K., 2016. Depression-like phenotype by deletion of α7 nicotinic acetylcholine receptor: role of BDNF-TrkB in nucleus accumbens. Sci. Rep. 6, 36705. https://doi.org/10.1038/srep36705.

Zhang, K., Fujita, Y., Chang, L., Qu, Y., Pu, Y., Wang, S., Shirayama, Y., Hashimoto, K., 2019a. Abnormal composition of gut microbiota is associated with resilience versus susceptibility to inescapable electric stress. Transl. Psychiatry 9 (1), 231. https://doi.org/10.1038/s41398-019-0571-x.

Zhang, K., Yang, C., Chang, L., Sakamoto, A., Suzuki, T., Fujita, Y., Qu, Y., Wang, S., Pu, Y., Tan, Y., Hashimoto, K., 2020b. Essential role of microglial transforming growth factor-β1 in antidepressant actions of (*R*)-ketamine and the novel antidepressant TGF-β1. Transl. Psychiatry 10 (1), 32. https://doi.org/10.1038/s41398-020-0733-x.

Zhang, K., Sakamoto, A., Chang, L., Qu, Y., Wang, S., Pu, Y., Tan, Y., Wang, X., Fujita, Y., Ishima, T., Hatano, M., Hashimoto, K., 2021. Splenic NKG2D confers resilience versus susceptibility in mice after chronic social defeat stress: beneficial effects of (*R*)-ketamine. Eur. Arch. Psychiatry Clin. Neurosci. 271 (3), 447–456. https://doi.org/10.1007/s00406-019-01092-z.

Zhang, L., Zhang, J., You, Z., 2018. Switching of the microglial activation phenotype is a possible treatment for depression disorder. Front. Cell Neurosci. 12, 306. https://doi.org/10.3389/fncel.2018.00306.

Zhang, Y., Kutateladze, T.G., 2018. Diet and the epigenome. Nat. Commun. 9 (1), 3375. https://doi.org/10.1038/s41467-018-05778-1.

Zhang, Y., Huang, R., Cheng, M., Wang, L., Chao, J., Li, J., Zheng, P., Xie, P., Zhang, Z., Yao, H., 2019b. Gut microbiota from NLRP3-deficient mice ameliorates depressive-like behaviors by regulating astrocyte dysfunction via circHIPK2. Microbiome 7 (1), 116. https://doi.org/10.1186/s40168-019-0733-3.

Zheng, D., Liwinski, T., Elinav, E., 2020a. Interaction between microbiota and immunity in health and disease. Cell Res 30 (6), 492–506. https://doi.org/10.1038/s41422-020-0332-7.

Zheng, P., Wang, Y., Chen, L., Yang, D., Meng, H., Zhou, D., Zhong, J., Lei, Y., Melgiri, N. D., Xie, P., 2013. Identification and validation of urinary metabolite biomarkers for major depressive disorder. Mol. Cell Proteom. 12 (1), 207–214. https://doi.org/10.1074/mcp.M112.021816.

Zheng, P., Zeng, B., Zhou, C., Liu, M., Fang, Z., Xu, X., Zeng, L., Chen, J., Fan, S., Du, X., et al., 2016. Gut microbiome remodeling induces depressive-like behaviors through a pathway mediated by the host's metabolism. Mol. Psychiatry 21 (6), 786–796. https://doi.org/10.1038/mp.2016.44.

Zheng, P., Yang, J., Li, Y., Wu, J., Liang, W., Yin, B., Tan, X., Huang, Y., Chai, T., Zhang, H., 2020b. Gut microbial signatures can discriminate unipolar from bipolar depression. Adv. Sci. 7 (7), 1902862 https://doi.org/10.1002/advs.201902862.

Zhu, B., Wang, X., Li, L., 2010. Human gut microbiome: the second genome of human body. Protein Cell 1 (8), 718–725. https://doi.org/10.1007/s13238-010-0093-z.

Zhu, S., Jiang, Y., Xu, K., Cui, M., Ye, W., Zhao, G., Jin, L., Chen, X., 2020. The progress of gut microbiome research related to brain disorders. J. Neuroinflamm. 17 (1), 25. https://doi.org/10.1186/s12974-020-1705-z.