Microb Health Dis 2019; 1: e201

The microbiota-gut-brain axis in gastrointestinal inflammation and neurological comorbidities

T. Breugelmans[1,2], B. Y. De Winter[1,2], A. Smet[1,2]

[1]Laboratory of Experimental Medicine and Pediatrics, Faculty of Medicine and Health Sciences; [2]Infla-Med Research Consortium of Excellence, University of Antwerp, Antwerp, Belgium

Corresponding Author: Tom Breugelmans, MD; e-mail: tom.breugelmans2@uantwerpen.be

Abstract: This article reviews the main literature published between April 2018 and March 2019 in the field of the microbiota-gut-brain axis focusing on gastrointestinal inflammation and neurological comorbidities. Over the last year, further evidence emerged relating to the existence of a bidirectional link between gastrointestinal inflammation in the form of inflammatory bowel diseases (IBD) and infection on the one hand, and neuroinflammation and neuropsychological changes on the other. Gastric Helicobacter infection, for instance, provoked neuroinflammation, characterized by activated microglia, which resulted in short-term memory loss. Furthermore, whereas anxiety and depression were associated with increased activity or development of IBD, a diseased activity at baseline was associated with an increased risk of evoking abnormally anxious behaviour. Colitis induction in animal models, by inducing dysbiosis and intestinal barrier disruption, confirmed the effect on the brain and vice versa with a central role for the brain-derived neurotrophic factor (BDNF). In addition, toll-like receptor (TLR) signaling has emerged as an important communication platform between the microbiota, the gut, and the brain. More specifically, the absence of TLR4 in mice partially protected the animals from the Parkinson's disease-induced pathology. Furthermore, recent advances in the use of psychobiotics, referring to any exogenous influence whose effect on the brain is bacterially-mediated, highlighted an important role for *Lactobacillus* and *Bifidobacterium spp.*, heat-inactivated microbial fermentates, and natural herbs to treat gastrointestinal and neurological disorders.

Keywords: Microbiota-gut-brain axis, Dysbiosis, Inflammatory bowel diseases, Gastrointestinal infection, Parkinson's disease, Anxiety, Depression, Psychobiotics

THE MICROBIOTA-GUT-BRAIN AXIS IN GASTROINTESTINAL INFLAMMATORY DISORDERS

Microbiota-Gut-Brain Axis Dysfunction During Gastrointestinal Infection

In a study performed by Gorlé et al[1], *Helicobacter suis* infection induced inflammation in the stomach, but also in the brain which resulted in short-term memory loss. These alterations were accompanied by increased permeability of the gastrointestinal barrier, low-grade systemic inflammation, and disruption of the blood-cerebrospinal fluid (CSF) barrier, suggesting that *H. suis*-evoked increased gastrointestinal permeability and subsequent peripheral inflammation which induce changes *via* changes in the blood-CSF barrier integrity[1]. A further study investigating helminth infection with *Trichuris muris*, showed local colonic inflammation in adult mice which was accompanied by a shift in the microbiota composition with a higher abundance of *Bacteroidetes* and a decrease in *Firmicutes*. Behavioral and cognitive analyses performed at 9 months post-infection revealed deficits in spatial recognition memory and an anxiety-like behavioral phenotype in *Trichuris*-infected mice, which was associated with neuropathology and increased microglia activation in the brain[2].

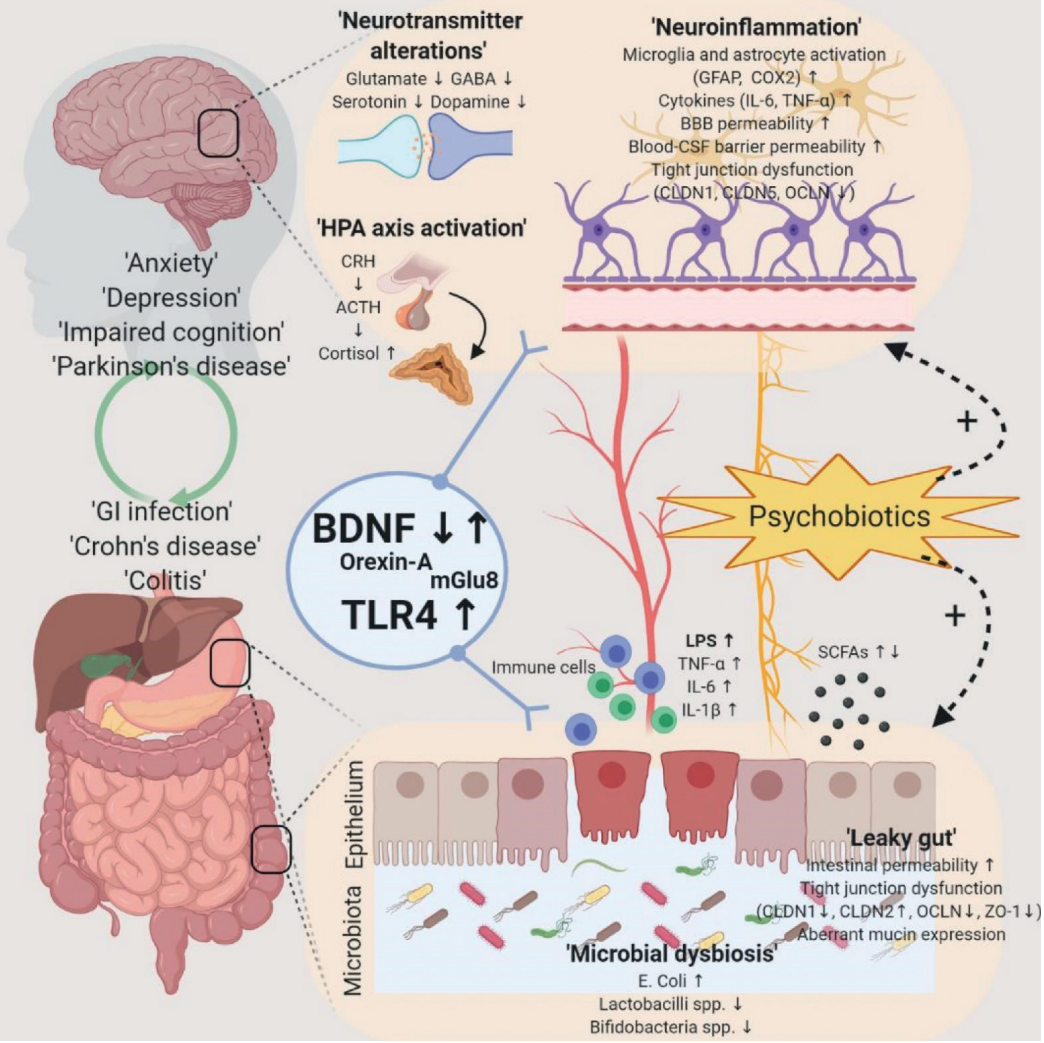

Figure 1. The microbiota-gut-brain axis in gastrointestinal (GI) inflammation and neurological comorbidities. Microbial dysbiosis, which often involves increased levels of Escherichia coli and reduced *Lactobacilli* and *Bifidobacteria spp.*, is associated with gastrointestinal inflammation and impaired intestinal barrier function, better known as a 'leaky gut'. The loss of the intestinal barrier integrity is characterized by increased permeability, tight junction dysfunction, and aberrant mucin expression. This will lead to elevated levels of LPS, pro-inflammatory cytokines, infiltration of immune cells, and changes in microbial metabolites, such as short-chain fatty acid (SCFAs). Via systemic routes and neural pathways, this will affect neurotransmitter levels, stimulate the hypothalamic-pituitary-adrenal (HPA) axis (stress response), affect brain barrier integrity, and induce neuroinflammation. In the opposite direction, brain homeostasis disturbance can have detrimental effects on the gut via similar mechanisms. The brain-derived neurotrophic factor (BDNF) and toll-like receptor 4 (TLR4) signaling pathways have emerged as central mediators of the bi-directional microbiota-gut-brain interactions during GI inflammation (due to infections or inflammatory disorders) and neurological abnormalities (anxiety, depression, impaired cognition, and Parkinson's disease). Additionally, several studies report a potential role for Orexin-A and mGlu8 as well. Increasing evidence further shows that psychobiotics, exert beneficial effects on gut and brain homeostasis by restoring the gut microbiota composition. (The figure was created with Biorender.com).

Microbiota-Gut-Brain Axis Dysfunction in Inflammatory Bowel Diseases

Inflammatory bowel diseases (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), are characterized by chronic relapsing intestinal inflammation, loss of intestinal barrier integrity, and microbial dysbiosis[3]. These disease entities have also been associated with mood disorders, such as anxiety or depression, but it is not clear whether one contributes to development of the other, or if the interaction is bidirectional (i.e., anxiety or depression contributes to the progression of IBD and IBD affect psychological health). This was further investigated in a 2-year longitudinal prospective study of 405 patients with CD or UC. Increased CD or UC disease activity at baseline was

associated with an almost 6-fold increased risk for subsequent abnormal anxiety scores, whereas in patients with quiescent IBD at baseline, abnormal anxiety scores were associated with later need for glucocorticosteroid prescription or flare of IBD activity[4]. Another study evaluated clinical data from 403,665 patients with new-onset depression and from 5,323,986 individuals without a history of depression. After controlling demographic and clinical covariates, it was shown that a history of depression increased the risk of developing IBD. Interestingly, antidepressant therapy partially protected these patients from developing IBD, especially UC[5]. Lv et al[6] analysed neurotransmitter metabolites using proton magnetic resonance spectroscopy in CD patients that suffered from abdominal pain. The net finding revealed elevated glutamate and decreased levels of gamma-aminobutyric acid (GABA) in the anterior cingulate cortex. This imbalance in glutamate and GABA may imply disturbances of the intestinal microbiota, which have been previously shown to modulate the levels of neurotransmitters and their receptors, and play a key role in abdominal pain processing for patients with CD[6]. Furthermore, gut microbiota can affect human behavior and mood as shown by recent studies describing an altered microbiota composition in patients with depression[7-9]. Whereas Chung et al[7] found an overrepresentation of both *Firmicutes* and *Actinobacteria,* Huang et al[8] reported a decreased abundance of *Firmicutes* in patients with major depressive disorder. The former study corrected for dietary patterns, which could potentially (partially) explain the conflicting results observed in both studies. Another study investigated the covariation of microbiota composition with quality of life (QoL) indicators and depression in two large population cohorts. *Faecalibacterium* and *Coprococcus* positively correlated with several QoL indicators. Additionally, *Coprococcus* was also depleted in depression[9]. Both genera are members of the phylum Firmicutes and produce butyrate, which has been shown to enforce the intestinal barrier and to alleviate intestinal inflammation[10]. The above studies clearly emphasize a bidirectional link between gastrointestinal alterations and changes in mood, cognition, and pain perception.

Studies investigating the underlying mechanisms involved in microbiota-gut-brain axis dysfunction in IBD remain scarce. A study by Jang et al[11] showed that trinitrobenzene sulphonic acid (TNBS)-induced colitis in mice was associated with loss of intestinal barrier integrity, an increase in *Enterobacteriaceae* (e.g. *Escherichia coli*), a decrease in *Lactobacillus johnsonii*, increased fecal and blood levels of lipopolysaccharides (LPS), increased tumor necrosis factor-α (TNF-α) expression in plasma and hippocampus, impaired learning and memory. The treatment with *E. coli*, which was isolated from the feces of mice with TNBS-induced colitis, induced similar effects. This suggests that chronic endotoxemia, as a result of increased LPS production by the gut microbiota, evoked systemic inflammation and neuroinflammation as shown by NF-κB activation, increased TNF-α expression, and suppressed brain-derived neurotrophic factor (BDNF) expression in the hippocampus[11]. BDNF is widely expressed in the brain and gut and modulates neuroplasticity, inflammation, and gut homeostasis[12-14]. On the contrary, Luo et al[15] reported that *E. coli* LPS induced anti-depressive effects in the germ-free mice by modulating the glucocorticoid pathway. In a dextran sodium sulphate (DSS)-induced acute colitis mouse model, elevated plasma levels of IL-6 resulted in microglia activation in the brain cortex, which was associated with a mild disruption of the blood brain barrier (BBB) as shown by occludin (OCLN) and claudin (CLDN)5 dysfunction in both the cortex and hippocampus[16]. Nyuyki et al[17] demonstrated an increased anxiety and reduced locomotion in mice suffering from DSS-induced colitis. Furthermore, DSS-treated mice developed faster seizures, provoked by intraperitoneal injection of kainic acid, which is indicative for an increased CNS excitability due to colitis. Another study examined brain-specific changes in the expression of neuroinflammatory markers and the involvement of the hypothalamic-pituitary-adrenal (HPA) axis in DSS-induced colitis mice. They found an early and sustained increase in the expression of the glial fibrillary acidic protein (GFAP), which is implicated in maintaining the BBB integrity and the stability of astrocytes, and cyclooxygenase 2 (COX-2) (a cyclooxygenase involved in prostaglandin synthesis) in the hippocampus of colitis mice. These elevations preceded the activation of the HPA axis, as assessed by measuring C-reactive protein (CRP) and corticosterone levels in the plasma, suggesting that hippocampal damage occurred in a glucocorticoid independent way. Further evaluation of BDNF and COX-2 levels revealed a rapid increase of BDNF and COX-2 in the hypothalamus whereas BDNF expression was decreased in the amygdala[18]. Defective BDNF signaling was found to drastically affect the microbial composition and gastrointestinal integrity as proven by cluster analysis of bacterial genomic DNA subjected to a denaturing gradient gel electrophoresis and altered colonic expression of CLDN1, CLDN2, zonula occludens (ZO)-1, and OCLN[13].

Orexin-A, a neuroprotective agent known to be produced by hypothalamic neurons, was recently suggested as a central regulator of the gut-brain axis. In two different experimental approaches, i.e., *in vitro* challenging of Caco-2 monolayers and *in vivo* intraperitoneal injection of mice with the endotoxin LPS, Orexin-A pre-treatment was able to repress LPS-induced disruption of intestinal barrier integrity and microglia activation by stimulating the Orexin-A receptor 1 in the gut and in the brain[19].

INFLAMMATION-DRIVEN DYSBIOSIS IN PARKINSON'S DISEASE

Patients suffering from Parkinson's disease (PD) show decreased motor function and experience symptoms like tremor, bradykinesia, rigidity, and late postural instability, which is caused by a progressive loss of dopaminergic neurons in the substantia nigra pars compacta. Nowadays, the number of studies focusing on the role of the altered gut microbiota in the pathophysiology of PD is increasing, due to the observed coincidence of gastrointestinal complaints and PD development[20-24]. Dodiya et al[25] showed that chronic stress-induced intestinal barrier disruption in the rotenone PD mouse model exacerbated the course of PD *via* a dysfunctional microbiota-gut-brain axis. In a 1methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced mouse model of PD, the phylum *Proteobacteria* and orders *Turicibacterales* and *Enterobacteriales* were increased, whereas the phylum *Firmicutes* and the order *Clostridiales* were significantly decreased. This was associated with elevated short-chain fatty acid (SCFA) production, increased activation of astrocytes and microglia, loss of dopaminergic neurons, reduced levels of the neurotransmitters dopamine and serotonin, and reduced motor function[26,27]. These parameters could all partially be restored by fecal microbiota transplantation (FMT)[25] or by a fasting mimicking diet in the form of intermittent caloric restriction[27]. Moreover, FMT was able to partially repress the upregulation of toll-like receptor (TLR), TANK-binding kinase 1 (TBK1), and NF-κB in both the colon and striatum[26]. The TLR4 signaling pathway has emerged as a potent communication platform between the microbiota, the gut, and the brain. Upon intestinal barrier disruption and microbial dysbiosis, TLR4 receptor activation results in NF-κB and TNF-α upregulation, which are believed to not only induce peripheral inflammation but also promote neuroinflammation[20]. Perez-Pardo et al[20] showed that TLR4 KO mice are partially protected from the PD-induced pathology by rotenone treatment. More specifically, absence of TLR4 was associated with less intestinal inflammation, intestinal and motor dysfunction, neuroinflammation and neurodegeneration, relative to rotenone-treated wild-type animals, despite the presence of dysbiotic microbiota in TLR4 KO mice. These findings suggest that TLR4-mediated inflammation plays an important role in intestinal and/or brain inflammation, which may be one of the key factors leading to neurodegeneration in PD[20].

Modulating the glutamate neurotransmission pathway by targeting metabotropic glutamate receptors (mGlu) might also be a potential therapeutic target for PD. Glutamatergic neurotransmission has a fundamental role in both the CNS and ENS. Whereas previous research has highlighted the use of mGlu4 agonists for improving motor function in PD, a recent study[28] showed that a deficiency of mGlu8 was protective against locomotor, sensorimotor, and memory deficits induced by MPTP in mice and was associated with a decreased α-diversity of the microbiome. Since the microbiota is able to produce neurotransmitters and their precursors, including glutamate and glutamine, they could modulate glutamatergic signaling, especially in the case of impaired barrier function as observed in PD and IBD[20,29].

THE IMPACT OF PSYCHOBIOTICS ON THE MICROBIOTA-GUT-BRAIN AXIS FUNCTION

Recent studies in 2018, further support the potential use of probiotics on brain function and behavior in health and disease. In healthy volunteers, negative correlations were reported between *Lactobacillus* and *Bifidobacterium* abundance and subjective scoring of anxious and depressive feelings[30]. The same association was also shown in another study where the administration of a probiotic mixture containing several *Lactobacillus* and *Bifidobacterium* strains over a 4-week period to healthy participants was associated with an improvement of mood and cognition scores and changes in neural activity[31]. On the contrary, a study by Papalini et al[32] using a similar probiotic cocktail, only reported a protective effect on working memory performance after stress induction.

The importance and potential beneficial effects of *Lactobacillus* species for the treatment of stress, anxiety, and depression has also been demonstrated in many recent animal studies[33-39]. In one of these studies, a probiotic mixture of *L. reuteri*, *L. johnsonii*, *L. plantarum*, and *L. rhamnosus* was shown to reduce anxiety by restoring intestinal barrier integrity and alleviating both gastrointestinal inflammation and neuroinflammation[35]. Furthermore, in a follow-up study by the same authors, oral administration of *L. johnsonii* was associated with an increase in BDNF levels and CLDN5 expression in the hippocampus, whereas colon shortening, LPS production, and *Proteobacteria* levels were alleviated. In addition, proinflammatory cytokine expression and immune cell infiltration were suppressed in the hippocampus, blood, and colon[39]. In another study, patients with major depression were treated with *L. plantarum 299v* for 8 weeks. A modest improvement in cognitive functioning was reported. The authors speculated that *L. plantarum 299v* improved intestinal barrier function, which led to a reduction in kynurenines[40].

Although they did not observe significant alterations in cytokine and cortisol levels in the blood, it has previously been shown that kynurenines, which are produced from tryptophan (i.e., serotonin precursor), exerted detrimental effects on mood and cognition[41].

Different strains of *Bifidobacterium* were also shown to positively influence the course of depression in animal models by affecting hydroxytryptophan (5-HT) synthesis, the precursor of serotonin[42,43]. Furthermore, victims of a major flood disaster, that developed IBS-related mental health problems, reported an improved mental well-being after a 3-month-during therapy with *B. infantis*. This was associated with a restoration of the Firmicutes/Bacteroidetes balance in the gut[44].

Apart from *Lactobacillus* and *Bifidobacterium* strains, which received the most attention due to their favorable outcome in many animal studies, a study performed by Miyaoka et al[45] explored the probiotic potential of *Clostridium butyricum* in 40 patients with major depression that were resistant to conventional antidepressant therapy. *C. butyricum* is able to produce SCFAs and in this way could exert central effects. After 8-week supplementation, 70% of the patients receiving *Clostridium* displayed significant improvements, stated as a 50% reduction of the initial score on the Hamilton Depression Rating Scale (HAMD-17). Furthermore, 35% of the patients even achieved remission[45] which was based on a score of 7 or less on the HAMD-17[45]. Sun et al[46] suggested that these beneficial effects could be due to an increased Glucagon-Like Peptide (GLP)-1 secretion from intestinal epithelial cells upon *C. butyricum*-produced SCFA stimulation, as GLP-1 receptors are dispersed in the CNS and modulate neuronutrition and neuroprotection. Mice subjected to chronic unpredictable mild stress (CUMS) and treated with *C. butyricum* significantly improved CUMS-induced depressive-like behavior and showed restored levels of GLP-1 in the colon and 5-HT and BDNF in the brain[46]. Administration of *Faecalibacterium prausnitzii,* which has been reported to be reduced in IBD patients suffering from depression, was shown to alleviate behavioral changes, cytokine release, HPA axis activation, and to increase SCFA production after CUMS-induced depression[47]. Furthermore, the correlation of the microbiota composition with the QoL and depression was investigated in large independent human cohorts. Butyrate-producing *Faecalibacterium* and *Coprococcus* bacteria were consistently associated with higher quality of life indicators. Together with *Dialister*, *Coprococcus* spp. were also depleted in depression, even after correcting for the confounding effects of antidepressants and thus could be potential targets for future research[9].

Recently the term 'psychobiotics' was introduced, referring to any exogenous influence whose effect on the brain is bacterially-mediated. This definition would include inactivated microorganisms with anxiolytic and antidepressant effects or natural compounds metabolized by the gut microbiota. The addition of a heat-inactivated fermentate of *L. fermentum* and *L. delbrueckii* to the diet of healthy mice demonstrated increased sociability and lower baseline corticosterone levels. This diet also led to subtle but significant changes in the microbiota, with less abundant taxa being affected the most[48]. Similar antidepressant effects were also observed using the herb paeoniflorin[49].

CONCLUDING REMARKS

In this review, evidence was given for a bidirectional link between the microbiome, the gut, and the brain in gastrointestinal disorders and Parkinson's disease. Nevertheless, most suggestions concerning the existence of this link remain rather based on associations and thus future studies should focus on the underlying molecular mechanisms that are responsible for microbiota-gut-brain axis dysfunction. Microbial dysbiosis, in particular an increase of *E. coli* and decrease

of *Lactobacillus* and *Bifidobacterium spp.*, in combination with intestinal barrier dysfunction, seem to exert central effects by affecting systemic inflammation, SCFA production and BDNF, TLR4 and neurotransmitter signalling and vice versa. Moreover, recent studies further show that restoring the microbiota composition by the administration of psychobiotics offers interesting options to treat gastrointestinal and neurological disorders.

Conflict of Interest

The authors declare that they have no conflict of interest.

REFERENCES

1. Gorlé N, Blaecher C, Bauwens E, Vandendriessche C, Balusu S, Vandewalle J, Van Cauwenberghe C, Van Wonterghem E, Van Imschoot G, Liu C, Ducatelle R, Libert C, Haesebrouck F, Smet A, Vandenbroucke RE. The choroid plexus epithelium as a novel player in the stomach-brain axis during Helicobacter infection. Brain Behav Immun 2018; 69: 35-47.
2. Giacomin PR, Kraeuter AK, Albornoz EA, Jin S, Bengtsson M, Gordon R, Woodruff TM, Urich T, Sarnyai Z, Soares Magalhães RJ. Chronic Helminth Infection Perturbs the Gut-Brain Axis, Promotes Neuropathology, and Alters Behavior. J Infect Dis 2018; 218: 1511-1516.
3. Podolsky DK. Inflammatory Bowel Disease. N Engl J Med 2002; 347: 417-429.
4. Gracie DJ, Guthrie EA, Hamlin PJ, Ford AC. Bi-directionality of Brain–Gut Interactions in Patients With Inflammatory Bowel Disease. Gastroenterology 2018; 154: 1635-1646.e3.
5. Frolkis AD, Vallerand IA, Shaheen A-A, Lowerison MW, Swain MG, Barnabe C, Patten SB, Kaplan GG. Depression increases the risk of inflammatory bowel disease, which may be mitigated by the use of antidepressants in the treatment of depression. Gut 2019; 68: 1606-1612.
6. Lv K, Song W, Tang R, Pan Z, Zhang Y, Xu Y, Lv B, Fan Y, Xu M. Neurotransmitter alterations in the anterior cingulate cortex in Crohn's disease patients with abdominal pain: a preliminary MR spectroscopy study. NeuroImage Clin 2018; 20: 793-799.
7. Chung YCE, Chen HC, Chou HCL, Chen IM, Lee MS, Chuang LC, Liu YW, Lu ML, Chen CH, Wu CS, Huang MC, Liao SC, Ni YH, Lai MS, Shih WL, Kuo PH. Exploration of microbiota targets for major depressive disorder and mood related traits. J Psychiatr Res 2019; 111: 74-82.
8. Huang Y, Shi X, Li Z, Shen Y, Shi X, Wang L, Li G, Yuan Y, Wang J, Zhang Y, Zhao L, Zhang M, Kang Y, Liang Y. Possible association of Firmicutes in the gut microbiota of patients with major depressive disorder. Neuropsychiatr Dis Treat 2018; 14: 3329-3337.
9. Valles-Colomer M, Falony G, Darzi Y, Tigchelaar EF, Wang J, Tito RY, Schiweck C, Kurilshikov A, Joossens M, Wijmenga C, Claes S, Van Oudenhove L, Zhernakova A, Vieira-Silva S, Raes J. The neuroactive potential of the human gut microbiota in quality of life and depression. Nat Microbiol 2019; 4: 623-632.
10. Rivière A, Selak M, Lantin D, Leroy F, De Vuyst L. Bifidobacteria and butyrate-producing colon bacteria: Importance and strategies for their stimulation in the human gut. Front Microbiol 2016; 7: 979.
11. Jang SE, Lim SM, Jeong JJ, Jang HM, Lee HJ, Han MJ, Kim DH. Gastrointestinal inflammation by gut microbiota disturbance induces memory impairment in mice. Mucosal Immunol 2018; 11: 369-379.
12. Miranda M, Morici JF, Zanoni MB, Bekinschtein P. Brain-Derived Neurotrophic Factor: A Key Molecule for Memory in the Healthy and the Pathological Brain. Front Cell Neurosci 2019; 13: 363.
13. Li C, Cai YY, Yan ZX. Brain-derived neurotrophic factor preserves intestinal mucosal barrier function and alters gut microbiota in mice. Kaohsiung J Med Sci 2018; 34: 134-141.
14. Bistoletti M, Caputi V, Baranzini N, Marchesi N, Filpa V, Marsilio I, Cerantola S, Terova G, Baj A, Grimaldi A, Pascale A, Frigo G, Crema F, Giron MC, Giaroni C. Antibiotic treatment-induced dysbiosis differently affects BDNF and TrkB expression in the brain and in the gut of juvenile mice. PLoS One 2019; 14: e0212856.
15. Luo Y, Zeng B, Zeng L, Du X, Li B, Huo R, Liu L, Wang H, Dong M, Pan J, Zheng P, Zhou C, Wei H, Xie P. Gut microbiota regulates mouse behaviors through glucocorticoid receptor pathway genes in the hippocampus. Transl Psychiatry 2018; 8: 187.
16. Han Y, Zhao T, Cheng X, Zhao M, Gong S-H, Zhao Y-Q, Wu H-T, Fan M, Zhu L-L. Cortical Inflammation is Increased in a DSS-Induced Colitis Mouse Model. Neurosci Bull 2018; 34: 1058-1066.
17. Nyuyki KD, Cluny NL, Swain MG, Sharkey KA, Pittman QJ. Altered Brain Excitability and Increased Anxiety in Mice With Experimental Colitis: Consideration of Hyperalgesia and Sex Differences. Front Behav Neurosci 2018; 12: 58.
18. Do J, Woo J. From Gut to Brain: Alteration in Inflammation Markers in the Brain of Dextran Sodium Sulfate-induced Colitis Model Mice. Clin Psychopharmacol Neurosci 2018; 16: 422-433.
19. Tunisi L, Forte N, Fernández-Rilo AC, Mavaro I, Capasso R, D'Angelo L, Milić N, Cristino L, Di Marzo V, Palomba L. Orexin-A Prevents Lipopolysaccharide-Induced Neuroinflammation at the Level of the Intestinal Barrier. Front Endocrinol (Lausanne) 2019; 10: 219.
20. Perez-Pardo P, Dodiya HB, Engen PA, Forsyth CB, Huschens AM, Shaikh M, Voigt RM, Naqib A, Green SJ, Kordower JH, Shannon KM, Garssen J, Kraneveld AD, Keshavarzian A. Role of TLR4 in the gut-brain axis in Parkinson's disease: a translational study from men to mice. Gut 2019; 68: 829-843.
21. Lin A, Zheng W, He Y, Tang W, Wei X, He R, Huang W, Su Y, Huang Y, Zhou H, Xie H. Gut microbiota in patients with Parkinson's disease in southern China. Parkinsonism Relat Disord 2018; 53: 82-88.
22. Wang S, Li N, Zou H, Wu M. Gut microbiome-based secondary metabolite biosynthetic gene clusters detection in Parkinson's disease. Neurosci Lett 2019; 696: 93-98.

23. Qian Y, Yang X, Xu S, Wu C, Song Y, Qin N, Chen S-D, Xiao Q. Alteration of the fecal microbiota in Chinese patients with Parkinson's disease. Brain Behav Immun 2018; 70: 194-202.
24. Barichella M, Severgnini M, Cilia R, Cassani E, Bolliri C, Caronni S, Ferri V, Cancello R, Ceccarani C, Faierman S, Pinelli G, Bellis G, Zecca L, Cereda E, Consolandi C, Pezzoli G. Unraveling gut microbiota in Parkinson's disease and atypical parkinsonism. Mov Disord 2019; 34: 396-405.
25. Dodiya HB, Forsyth CB, Voigt RM, Engen PA, Patel J, Shaikh M, Green SJ, Naqib A, Roy A, Kordower JH, Pahan K, Shannon KM, Keshavarzian A. Chronic stress-induced gut dysfunction exacerbates Parkinson's disease phenotype and pathology in a rotenone-induced mouse model of Parkinson's disease. Neurobiol Dis 2018: 104352. doi: 10.1016/j.nbd.2018.12.012. [Epub ahead of print].
26. Sun MF, Zhu YL, Zhou ZL, Jia XB, Xu YD, Yang Q, Cui C, Shen YQ. Neuroprotective effects of fecal microbiota transplantation on MPTP-induced Parkinson's disease mice: gut microbiota, glial reaction and TLR4/TNF-αsignaling pathway. Brain Behav Immun 2018; 70: 48-60.
27. Zhou ZL, Jia XB, Sun MF, Zhu YL, Qiao CM, Zhang BP, Zhao LP, Yang Q, Cui C, Chen X, Shen YQ. Neuroprotection of Fasting Mimicking Diet on MPTP-Induced Parkinson's Disease Mice via Gut Microbiota and Metabolites. Neurotherapeutics 2019: 1-20.
28. Torres ERS, Akinyeke T, Stagaman K, Duvoisin RM, Meshul CK, Sharpton TJ, Raber J. Effects of Sub-Chronic MPTP Exposure on Behavioral and Cognitive Performance and the Microbiome of Wild-Type and mGlu8 Knockout Female and Male Mice. Front Behav Neurosci 2018; 12: 140.
29. Baj A, Moro E, Bistoletti M, Orlandi V, Crema F, Giaroni C. Glutamatergic Signaling Along The Microbiota-Gut-Brain Axis. Int J Mol Sci 2019; 20: 1482.
30. Taylor AM, Thompson S V., Edwards CG, Musaad SMA, Khan NA, Holscher HD. Associations among diet, the gastrointestinal microbiota, and negative emotional states in adults. Nutr Neurosci 2019: 1-10.
31. Bagga D, Reichert JL, Koschutnig K, Aigner CS, Holzer P, Koskinen K, Moissl-Eichinger C, Schöpf V. Probiotics drive gut microbiome triggering emotional brain signatures. Gut Microbes 2018; 9: 486-496.
32. Papalini S, Michels F, Kohn N, Wegman J, Hemert S van, Roelofs K, Arias-Vasquez A, Aarts E. Stress matters: Randomized controlled trial on the effect of probiotics on neurocognition. Neurobiol Stress 2019; 10.
33. Li N, Wang Q, Wang Y, Sun A, Lin Y, Jin Y, Li X. Oral Probiotics Ameliorate the Behavioral Deficits Induced by Chronic Mild Stress in Mice via the Gut Microbiota-Inflammation Axis. Front Behav Neurosci 2018; 12: 266.
34. Partrick KA, Chassaing B, Beach LQ, McCann KE, Gewirtz AT, Huhman KL. Acute and repeated exposure to social stress reduces gut microbiota diversity in Syrian hamsters. Behav Brain Res 2018; 348: 277.
35. Jang HM, Lee HJ, Jang SE, Han MJ, Kim DH. Evidence for interplay among antibacterial-induced gut microbiota disturbance, neuro-inflammation, and anxiety in mice. Mucosal Immunol 2018; 11: 1386-1397.
36. Cowan CSM, Richardson R. Early-life stress leads to sex-dependent changes in pubertal timing in rats that are reversed by a probiotic formulation. Dev Psychobiol 2019; 61: 679-687.
37. Getachew B, Reyes RE, Davies DL, Tizabi Y. Moxidectin Effects on Gut Microbiota of Wistar-Kyoto Rats: Relevance to Depressive-Like Behavior. Clin Pharmacol Transl Med 2019; 3: 134-142.
38. Mohammadi G, Dargahi L, Naserpour T, Mirzanejad Y, Alizadeh SA, Peymani A, Nassiri-Asl M. Probiotic mixture of Lactobacillus helveticus R0052 and Bifidobacterium longum R0175 attenuates hippocampal apoptosis induced by lipopolysaccharide in rats. Int Microbiol 2018: 1-7.
39. Jang HM, Lee KE, Lee HJ, Kim DH. Immobilization stress-induced Escherichia coli causes anxiety by inducing NF-κB activation through gut microbiota disturbance. Sci Rep 2018; 8: 13897.
40. Rudzki L, Ostrowska L, Pawlak D, Małus A, Pawlak K, Waszkiewicz N, Szulc A. Probiotic Lactobacillus Plantarum 299v decreases kynurenine concentration and improves cognitive functions in patients with major depression: A double-blind, randomized, placebo controlled study. Psychoneuroendocrinology 2019; 100: 213-222.
41. Lovelace MD, Varney B, Sundaram G, Lennon MJ, Lim CK, Jacobs K, Guillemin GJ, Brew BJ. Recent evidence for an expanded role of the kynurenine pathway of tryptophan metabolism in neurological diseases. Neuropharmacology 2017; 112: 373-388.
42. Tian P, Wang G, Zhao J, Zhang H, Chen W. Bifidobacterium with the role of 5-hydroxytryptophan synthesis regulation alleviates the symptom of depression and related microbiota dysbiosis. J Nutr Biochem 2019; 66: 43-51.
43. Guo Y, Xie JP, Deng K, Li X, Yuan Y, Xuan Q, Xie J, He XM, Wang Q, Li JJ, Luo HR. Prophylactic Effects of Bifidobacterium adolescentis on Anxiety and Depression-Like Phenotypes After Chronic Stress: A Role of the Gut Microbiota-Inflammation Axis. Front Behav Neurosci 2019; 13: 126.
44. Ma ZF, Yusof N, Hamid N, Lawenko RM, Mohammad WMZW, Liong MT, Sugahara H, Odamaki T, Xiao J, Lee YY. Bifidobacterium infantis M-63 improves mental health in victims with irritable bowel syndrome developed after a major flood disaster. Benef Microbes 2019; 10: 111-120.
45. Miyaoka T, Kanayama M, Wake R, Hashioka S, Hayashida M, Nagahama M, Okazaki S, Yamashita S, Miura S, Miki H, Matsuda H, Koike M, Izuhara M, Araki T, Tsuchie K, Azis IA, Arauchi R, Abdullah RA, Oh-Nishi A, Horiguchi J. Clostridium butyricum MIYAIRI 588 as Adjunctive Therapy for Treatment-Resistant Major Depressive Disorder: A Prospective Open-Label Trial. Clin Neuropharmacol 2018; 41: 151-155.
46. Sun J, Wang F, Hu X, Yang C, Xu H, Yao Y, Liu J. Clostridium butyricum Attenuates Chronic Unpredictable Mild Stress-Induced Depressive-Like Behavior in Mice via the Gut-Brain Axis. J Agric Food Chem 2018; 66: 8415-8421.
47. Hao Z, Wang W, Guo R, Liu H. Faecalibacterium prausnitzii (ATCC 27766) has preventive and therapeutic effects on chronic unpredictable mild stress-induced depression-like and anxiety-like behavior in rats. Psychoneuroendocrinology 2019; 104: 132-142.
48. Warda AK, Rea K, Fitzgerald P, Hueston C, Gonzalez-Tortuero E, Dinan TG, Hill C. Heat-killed lactobacilli alter both microbiota composition and behaviour. Behav Brain Res 2019; 362: 213-223.
49. Yu JB, Zhao ZX, Peng R, Pan LB, Fu J, Ma SR, Han P, Cong L, Zhang ZW, Sun LX, Jiang JD, Wang Y. Gut Microbiota-Based Pharmacokinetics and the Antidepressant Mechanism of Paeoniflorin. Front Pharmacol 2019; 10: 268.