Gut-brain axis and immunoneuroendocrine modulation in neurological and psychiatric disorders: A systematic review

Abstract
The present study aimed to explore the influence of the gut-brain axis on neuroendocrine and immunological modulation in neurological and psychiatric disorders. This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines, and searches were conducted in the electronic databases PubMed and SciELO using combinations of descriptors “Gastrointestinal Microbiome”, “Neurosecretory Systems”, “Immune Response”, “Nervous System Diseases” e “Mental Disorders”. From the 144 studies generated by crossing the descriptors, 32 of them were excluded because they were duplicated in the databases, 13 because they were not related to the objectives of the review, and another 29 because they were not on eligibility criteria. Therefore, 70 studies were included in the present review. Communication between the GI tract and the CNS occurs via the neuronal, endocrine, and immunological pathways through a) the production of neurotransmitters, b) the tryptophan metabolism, c) the modulation of the immunological activity in the CNS and SNE, d) production of short chain fatty acids, e) the production of intestinal hormones, and f) the production of branched chain amino acids.

Keywords: Gastrointestinal microbiome; Active immune response; Mental disorders; Neurosecretory systems; Nervous system diseases.

Resumo
O presente estudo teve como objetivo explorar a influência do eixo cérebro-intestino na modulação neuroendócrina e imunológica em distúrbios neurológicos e psiquiátricos. Esta revisão sistemática seguiu as diretrizes de Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA), e as pesquisas foram realizadas nas bases de dados eletrônicas PubMed e SciELO usando combinações dos descritores Gastrointestinal Microbiome, Neurosecretory Systems, Immune Response, Nervous System Diseases e Mental Disorders. A partir dos 144 estudos gerados pelo cruzamento dos descritores, 32 foram excluídos por estarem duplicados nas bases de dados, 13 por não estarem relacionados aos objetivos da revisão e outros 29 por não atenderem aos critérios de elegibilidade selecionados. Portanto, 70 estudos foram incluídos na presente revisão. A comunicação entre o trato gastrintestinal e o SNC ocorre através das vias neuronal, endócrina e imunológica por meio de a) produção de neurotransmissores, b) metabolismo do triptofano, c) modulação da atividade imunológica no SNC e SNE, d) produção de ácidos graxos de cadeia curta, e) a produção de hormônios intestinais e f) a produção de aminoácidos de cadeia ramificada.
Palavras-chave: Microbioma gastrointestinal; Resposta imune ativa; Transtornos mentais; Sistemas neurosecretorios; Doenças do sistema nervoso.

Resumen
El presente estudio tuvo como objetivo explorar la influencia del eje cerebral-intestino en la modulación neuroendocrina e inmunológica en trastornos neurológicos y psiquiátricos. Esta revisión sistemática siguió las pautas...
de Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA), y las búsquedas se realizaron en las bases de datos electrónicas PubMed y SciELO utilizando combinaciones del Gastrointestinal Microbiome, Neurosecretory Systems, Immune Response, Nervous System Diseases and Mental Disorders. De los 144 estudios generados por el cruce de descriptores, 32 fueron excluidos por estar duplicados en las bases de datos, 13 por no estar relacionados con los objetivos de la revisión y otros 29 por no cumplir con los criterios de elegibilidad seleccionados. Por lo tanto, se incluyeron 70 estudios en la presente revisión. La comunicación entre el tracto gastrointestinal y el SNC se produce a través de vías neuronales, endocrinas e inmunológicas a través de a) producción de neurotransmisores, b) metabolismo del triptófano, c) modulación de la actividad inmunitaria en el SNC y SNE, d) producción de ácidos grasos de cadena corta, e) la producción de hormonas intestinales, y f) la producción de aminoácidos de cadena ramificada.

**Palabras clave:** Microbioma gastrointestinal; Inmunidad activa; Trastornos mentales; Sistemas neurosecretores; Enfermedades del sistema nervioso.

1. Introduction

The human intestine comprises an impressive number of microorganisms that are estimated to contain 150 times more genes than the human genome itself. This population is composed of fungi, archaea, viruses, and bacteria, with a predominance of phyla Bacteroidetes, Firmicutes, Actinobacteria and Proteobacteria (Cho & Blaser, 2012).

Neurological and psychiatric disorders affect thousands of people, regardless of age or social class, in all regions of the world, representing about 12% of all global diseases (Vigo, et al., 2019). It is known that bidirectional communication between the brain and the intestine occurs through the neuronal (Cryan & O’Mahony, 2011), endocrine (Morowitz, et al., 2011), and immunological pathways (Belkaid & Hand, 2014; Duerkop, et al, 2009), corroborating the hypothesis that imbalances in this communication can impact the development of these disorders.

Animal and human model studies have been exploring the influence of the communication pathways between the gastrointestinal tract (GI) and the central nervous system (CNS), which make up the gut-brain axis, in the multi-causal picture of these disorders (Bravo, et al., 2011; Berer, et al., 2017). Several mechanisms have been proposed to explain this relationship, but little is known about the real influence of the trillions of microorganisms present in the intestinal microbiota on neuroendocrine and immunological modulation and the impact on neurological and psychiatric disorders (Bourassa, et al., 2016).

The present study aimed to explore the influence of the gut-brain axis on neuroendocrine and immunological modulation in neurological and psychiatric disorders.

2. Methodology

The data collected for the present systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses – PRISMA (2015) guidelines and the procedures for the survey, selection and evaluation stages of the studies are illustrated in Figure 1.
Search strategy

We executed a bibliographic review using systematic search elements to explore and explain experiments available in the databases (Pereira, et al., 2018). Searches were conducted in the electronic databases PubMed and SciELO using combinations of descriptors “Gastrointestinal Microbiome”, “Neurosecretory Systems”, “Immune Response”, “Nervous System Diseases” e “Mental Disorders”, respecting the particularities of the databases. The descriptors were selected in the Medical Subject Headings (MeSH) and the searches in the databases took place in January 2020.

Eligibility

The following criteria were used for studies inclusion or exclusion in this review: a) Articles published in indexed journals; b) Articles published in English, between 2000 and 2020; c) randomized clinical trials, with humans or animal models for neurological and psychiatric disorders; d) Microbiome studies involving or not the use of prebiotic or probiotic formulations, genetic predisposition, diet, use of medications and association with other diseases; e) studies that sought to demonstrate the role of the intestinal microbiota in neuroendocrine and immunological modulation and the impact on neuropsychiatric disorders.

3. Results and Discussion

From a total of 144 articles generated by crossing the descriptors, 32 were excluded because they were duplicated in the databases, and another 13 because they were not related to the objectives of the review. From the full-text studies evaluated for eligibility, (i) non-indexed articles were removed; (ii) published outside the 2000 and 2020 period; (iii) that were not clinical trials with humans or animal models; (iv) that did not explore the relationship between intestinal microbiota and neuropsychiatric disorders. Finally, 70 studies were included in the present review.

Microbiota-gut-brain axis signalling
Communication between the GI tract and the CNS occurs via the neuronal, endocrine and immunological pathways through a) the production of neurotransmitters, b) the tryptophan metabolism, c) the modulation of the immunological activity in the CNS and the SNE, d) production of short chain fatty acids, e) the production of intestinal hormones, and f) the production of branched chain amino acids, as seem at Figure 2 (Bohórquez, et al., 2015; Clarke, et al., 2013; Erny, et al., 2015; Macfarlane & Macfarlane, 2012; Vijay & Morris, 2014; Yang, et al., 2016; Yano, et al., 2015).

Figure 2. Microbiota-gut-brain axis – The intestinal microbiota is capable of producing the neurotransmitters serotonin (5-HT), γ-aminobutyric acid (GABA), dopamine and noradrenaline; tryptophan, a serotonin precursor amino acid; influencing the integrity of the intestinal epithelium, which controls the passage of immune signaling molecules, modulating this activity at a central and peripheral level; of producing short-chain fatty acids, which interact with immune and neuronal cells through monocarboxylate transporters; intestinal hormones, whose receptors are expressed in the CNS and GI tract; branched chain amino acids, which favor the link between the bacterial lipopolysaccharide and immune cells.
Synthesis of neurotransmitters and metabolism of tryptophan

In the study performed by Asano et al. (2012), reduced levels of norepinephrine and dopamine were identified in the cecum of mice raised in a sterile environment. Mice reared under the same conditions also had low levels of the amino acid tyrosine and high brain levels of dopamine, compared to the others (Matsumoto, et al., 2013; Nishino, et al., 2013). Furthermore, it was verified that the Helicobacter pylori bacterium can influence the levels of L-DOPA, a precursor molecule of dopamine (Pierantozzi, et al., 2006).

Lactobacillus and Bifidobacterium strains, especially L. brevis and B. dentium, proved to be excellent producers of GABA, the main CNS inhibitory neurotransmitter (Barrett, et al., 2012). The administration of Lactobacillus rhamnosus seems to alter the expression of GABA transporters, present in the blood-brain barrier (BBB), reducing the behavior of anxiety and depression observed in mice (Bravo, et al., 2011).

Clarke et al. (2013) associates the low plasma levels of serotonin in mice raised in a sterile environment, to the reduction of the expression of tryptophan hydroxylase, an enzyme that according to Yano et al. (2015) modulates the synthesis of serotonin. Desbonnet et al. (2008) reports an increase in tryptophan plasma levels, a precarious amino acid of serotonin, after the administration of B. anfantis. Valladares et al. (2013) reports an increase in the levels of serotonin itself after the administration of Lactobacillus johnsonii.

Immunological signaling

Erny et al. (2015) showed that the absence of a diversified microbiota significantly impacts the processes of activation, differentiation, and maintenance of microgliocytes, and that this impact can be reversed after a recolonization of the microbiota.

Also, the integrity of the intestinal mucosa influences the exchange of molecules and allows the immunological recognition of own and non-own antigens (Duerkop, et al., 2009). The bacterial lipopolysaccharide (LPS) crosses the epithelial barrier of the intestine and, in stressful situations, activates Toll-like receptors (TLRs) in the cells of the innate immune system (Maes, et al., 2008). Neonatal exposure to LPS has also been shown to enable prostaglandin-mediated HHA axis reactivity to LPS in adulthood (Mouihate, et al., 2010).

Short-chain fatty acids

Short chain fatty acids (SCFAs) produced by the bacterial fermentation of proteins and carbohydrates in the intestine (Macfarlane & Macfarlane, 2012), reach and act centrally through the monocarboxylate transporters expressed in the BBB (Vijay & Morris, 2014; Kekuda, et al., 2013).

Studies suggest that butyric, acetic, and propionic acids directly affect brain function and behavior. Butyric and propionic acids modulate the activity of tyrosine hydroxylase, an enzyme responsible for converting tyrosine into L-DOPA, a dopamine precursor molecule, impacting the synthesis of dopamine and norepinephrine (DeCastro, et al., 2005; Nankova, et al., 2014; Stilling, et al., 2016). Propionic acid is also capable of modulating serotonergic neurotransmission (Nankova, et al., 2014). SCFAs also have an impact on the maturation processes and function of microgliocytes, immune cells resident in the CNS (Huuskonen, et al., 2004; Erny, et al., 2015).

Enteroendocrine signaling

Enteroendocrine cells (EECs) have a significant influence on intestinal homeostasis. Enteroendocrine L cells (ELCs) and enterochromaffin cells (ECs) are the most abundant EECs and seem to play a role in the communication between brain and intestine (Bohórquez, et al., 2015).
ELCs secrete GLP-1 and PYY, potent anorectic hormones involved in the modulation of food, whose receptors are expressed in the intestine and the CNS; in the intestine, the activation of ELCs is triggered almost exclusively by bacterial metabolites (Elinav, et al., 2011). Bacterial LPS was shown to be able to induce GLP-1 secretion via ELCs (Larraufie, et al., 2017).

ECs produce a large part of systemic serotonin, which in turn activates numerous receptors present in intrinsic and extrinsic nerve fibers to the gastrointestinal tract, in addition to mediating peristalsis, some secretions, pain perception, inflammation and inflammatory responses (Mawe & Hoffman, 2013). Still, there are studies that suggest that secondary bile acids and bacterial LPS itself can modulate serotonin secretion via ECs (Kidd, et al., 2009).

**Branched-chain amino acids**

The branched chain amino acids (BCAAs) valine, leucine, and isoleucine are essential amino acids involved in insulin synthesis, cerebral amino acid absorption and immune modulation (Brosnan & Brosnan, 2006; Fernstrom, 2005).

Intestinal bacteria are responsible for part of the production of BCAAs present in the human body (Dai, et al., 2011; Blachier, et al., 2007). Yang et al. (2016) showed that BCAA formulations contributed to the decrease of bacteria from the phylum Firmicutes and growth of bacteria from the phylum Bacteroidetes - the decrease in the latter has been shown to impair the link between bacterial LPS and immune cells.

**Gut-brain axis neurological and psychiatric disorders**

Recent studies on neurological and psychiatric disorders and their relationship with intestinal microbiota are described and summarized in Table 1.

Table 1. Comparison of neuropsychiatric disorders and prebiotics and probiotics administration from recent literature.

| Disorder            | Study model | Bacterial species intervention                          | Main findings                                                                 | Author                        |
|---------------------|-------------|--------------------------------------------------------|-------------------------------------------------------------------------------|-------------------------------|
| **Neurological disorders** |             |                                                        |                                                                               |                               |
| Epilepsy            | Humans      | *Lactobacillus*, *Bifidobacterium*                    | Reduction in seizure frequency and improved quality of life in individuals resistant to antiepileptics | Gómez-Eguílaz, et al., 2018   |
| Parkinson's disease | Humans      | *Lactobacillus acidophilus*, *L. reuteri*, *L. fermentum*, *Bifidobacterium bifidum*, | Improvement in disease symptoms and reduction of C-reactive protein           | Tamtaji, et al., 2019a        |
| Alzheimer disease   | Humans      | *Bifidobacterium* spp., *Lactobacillus* spp.          | Improvement of cognitive function and metabolic status in Alzheimer's patients | Leblhuber, et al., 2018       |
|                     | Humans      | *Lactobacillus acidophilus*, *Bifidobacterium bifidum*, *B. longum* | Less intestinal permeability and abundance of *Faecalibacterium praunstii* compared to controls. | Tamtaji, et al., 2019b        |
| Multiple sclerosis  | *Lactobacillus*, *Bifidobacterium*, *Streptococcus*   | Increase in species number and induction of peripheral immune response        | Tankou, et al., 2018           |
| Psychiatric disorders                                      | Rats               | Bifidobacterium infantis + citalopram | Decreased peripheral levels of cytokines and corticotropin | Desbonnet, et al., 2010 |
|-----------------------------------------------------------|--------------------|--------------------------------------|----------------------------------------------------------|--------------------------|
| Depression                                                | Rats               | Bifidobacterium animalis subsp. lactis | Reversal of the exacerbated hypothalamic-pituitary-adrenal axis response | Barouei, et al., 2012    |
| Rats                                                      | Lactobacillus farcininis | Reversal of the exacerbated hypothalamic-pituitary-adrenal axis response | Ait-Belgnaoui, et al., 2012                                |
| Rats                                                      | Lactobacillus helveticus + Bifidobacterium longum | Performance improvement in applied anxiety tests and decrease in free cortisol levels. | Messaoudi, et al., 2011 |
| Mice                                                      | Lactobacillus helveticus | Decreased anxiety, depending on the diet and the presence or absence of inflammation. | Ohland, et al., 2013 |
| Autism spectrum disorder                                  | Mice               | Lactobacillus rhamnosus              | Reduction of corticosterone levels and changes in GABA levels. | Liu, et al., 2015 |
| Humans                                                    | Bifidobacterium, Lactobacillus, Streptococcus spp. | Return of the Firmicutes and Bacteroidetes predominance | Tomova, et al., 2015 |
| Rats                                                      | Lactobacillus reuteri | Reversal of inflammation induced by bacterial LPS | Navarro, et al., 2016 |
| Humans                                                    | Lactobacillus rhamnosus, L.helveticus, L.reuteri, L.paracasei, Bifidobacterium infantis, B.longum, | Improvement of gastrointestinal problems seen in individuals with autism | de Angelis, et al., 2015 |
| Mice                                                      | Bacteroides fragilis | Increased expression of junction proteins in the intestinal epithelium | Hsiao, et al., 2013 |
| Schizophrenia                                             | Humans             | Bifidobacterium                      | Improvement in anxiety and depressive symptoms among schizophrenics | Okubo, et al., 2019 |
| Bipolar disorder                                          | Humans             | Lactobacillus spp., Bifidobacterium lactis | Reduction of readmissions of individuals after a manic episode | Dickerson, et al., 2018 |

GABA γ-aminobutyric acid; LPS lipopolysaccharide. Source: Authors.

Epilepsy

Peng et al. (2018) found a predominance of the bacterial genera Dorea, Coprobacillus, Ruminococcus, Akkermansia, Neisseria and Coprococcus in individuals resistant to antiepileptic drugs. He et al. (2017) also present a case report of a patient with Crohn's disease who received a fecal transplant and showed improvement in convulsive crisis, even after the interruption of treatment with sodium valproate.
Parkinson's disease

Scheperjans et al. (2015) point to a predominance of Enterobacteriaceae and decreased levels of bacteria of the Prevotellaceae family. Keshavarzian et al. (2015) also point to a predominance of *Faecalibacterium* and *Ralstonia* (Proteobacteria) genus among individuals with Parkinson and bacteria of the genera *Blautia*, *Coprococcus* and *Roseburia* among the controls. Hasegawa et al. (2015) also point out that Parkinson's patients have dysbiosis and decreased circulating levels of protein binding to the bacterial LPS.

Alzheimer disease

Larsen et al. (2008) and Jordal et al. (2009) found that Amyloid-β peptides, whose accumulation is characteristic in Alzheimer's disease, function as adhesive materials necessary for the protection of bacteria from the Firmicutes, Proteobacteria and Actinobacteria phyla against innate host immune defenses. La Rosa et al. (2019) also associate epithelial barrier dysfunction and dysbiosis, and a consequent reduction in the phagocytosis of A-β peptides.

Butyrate, as well as intermediate molecules formed during its synthesis process, such as lactate, succinate and formate, are absorbed in the intestinal lumen and used by some bacteria for their survival (Bourassa, et al., 2016; Cummings, et al., 2004). Bourassa et al. (2016) also suggest that butyrate is associated with brain health by favoring the growth of bacteria from the phylum Firmicutes, in addition to offering a neuroprotective effect by inhibiting histone deacetylase.

Multiple sclerosis

Miyake et al. (2015) indicate abundance of *Bifidobacterium* and *Streptococcus* and reduced levels of *Bacteroides*, *Faecalibacterium*, *Prevotella* and *Anaerostipes* among individuals with multiple sclerosis. Next years, Chen et al. (2016) observed a greater abundance of *Pseudomonas*, *Mycoplana*, *Haemophilus*, *Blautia* and *Dorea*; Jangi et al. (2016) confirm *Prevotella* and *Sutterella*; and Berer et al. (2017) found that the expression of the symptoms of the disease correlated with a significant increase in bacteria of the genus *Akkermansia*.

Depression

It was found that depression induced by maternal separation induces behavioral changes and in the immune and nervous systems (Vetulani, 2013). Akbaraly et al. (2009) report dysbiosis caused by low consumption of essential nutrients and increased chances of developing depression. Therefore, Turnbaugh et al. (2008) recommend the consumption of a diet rich in fiber, grains, and fish for individuals with depression or vulnerable to it.

Dinan et al. (2013), in a review study, also point to a reversal of the exacerbated response of the hypothalamic-pituitary-adrenal axis after administration of *Bifidobacterium infantiles*.

Autism spectrum disorder

*Faecalibacterium* predominance was reported in the feces of babies with autism, associated with the expression of genes involved in the interferon-γ and 1 signaling pathways (Inoue, et al., 2016). Srikantha and Mohajeri (2019) corroborate the findings of Li et al. (2017) since they verified an increase in bacterial LPS in individuals with ASD, which in addition to stimulating Toll 4 (TLR4) receptors in the SNE can reach the CNS via BBB and stimulate microgliocytes.

In a review study, Ding et al. (2017) and Fattorusso et al. (2019) also show that metabolites of the intestinal microbiota, such as phenol compounds produced by *Lactobacillus*, *Bifidobacterium*, *Clostridium difficile* and *C.histolyticum*, by some means also influence the development of autism.
Schizophrenia

Individuals with schizophrenia have a predominance of the *Anaerococcus* genus and low levels of the phylum Proteobacteria, when compared to healthy controls; also, the abundance of Ruminococcaceae was associated with mild symptoms of the disease (Nguyen, et al., 2019). Studies carried out in mice show that the antipsychotic olanzapine promotes intestinal dysbiosis, in addition to weight gain and cardiometabolic dysfunction (Davey, et al., 2013).

Bipolar disorder

Evans et al. (2017) point to reduced levels of Firmicutes and *Faecalibacterium* among individuals with bipolar disorder compared to healthy controls, while Boem and Amedei (2019) found that suicides among bipolar, depressive, and schizophrenic individuals had higher bacterial lipopolysaccharide levels than healthy controls.

State-of-the-art sequencing technologies have not only reduced the limitations found in cultivation methods but have also revealed new perspectives on the relationship between the intestinal microbiota and the development of diseases (Valverde & Mellado, 2013). However, this relationship is configured in a complex scenario, where some aspects need to be considered.

It is known that the composition of the intestinal microbiota varies between different populations. De Filippo et al. (2010) found that the microbiota of developed populations has obesogenic conditions superior to those of underdeveloped populations; in this sense, studies with different populations may present relevant perspectives on this association.

Most of the studies on the association between the intestinal microbiota and neuropsychiatric disorders are carried out in an animal model, or with small samples of humans. In this sense, considering the multifactorial nature of these disorders (Boem & Amedei, 2019), further studies with a considerable sample size and an assessment under environmental (such as diet) and genetic (predisposition and pharmacogenetic response to treatment) aspects are necessary to understand the real role that the microbiota plays in these multi-causal conditions.

It should be noted that the phenotypic heterogeneity of these disorders can also be explained by epigenetic factors (Uher, 2014; Landgrave-Gómez, et al., 2015). Inoue et al. (2016) report the association between *Faecalibacterium* genus, and the expression of genes involved in the IFN-γ and IFN-1 signaling pathways, but not enough is known about the real influence of the intestinal microbiota on epigenetic modulation.

4. Conclusion

This article has presented a systematic review about microbiota gut-brain axis influence through different pathways, such neuronal, endocrine, and immunological systems. Strong evidence suggests that specific microorganism species could shape the host gut-brain axis during neurological disorders. However, in all studies including patients or animal models, the exact mechanisms of action and signaling pathways activated by intestinal microbiota and their metabolites are still not completely elucidated.

Most of the studies found are realized in animal models, or with small human samples, and that considering the multifactorial character of neurological and psychiatric disorders, more epidemiological studies with a considerable sample size are needed, and that consider multiple sources of exposure (genetics, lifestyle, environmental) to better understand the influence of the microbiota on their multicausal condition.

References

Ait-Belgnaoui, A., Durand, H., Cartier, C., Chaumaz, G., Etutamene, H., & Theodorou, V. (2012). Prevention of gut leakiness by a probiotic treatment leads to attenuated HPA response to an acute psychological stress in rats. *Psychoneuroendocrinology*, 37(11), 1885-1895. 10.1016/j.psyneuen.2012.03.024
Liu, X., Cao, S., & Zhang, X. (2015). Modulation of Gut Microbiota-Brain Axis by Probiotics, Prebiotics, and Diet. *J Agric Food Chem*, 63(36), 7885-7895. 10.1021/acs.jafc.5b02404

Macfarlane, G. T., & Macfarlane, S. (2012). Bacteria, colonic fermentation, and gastrointestinal health. *J AOAC Int*, 95(1), 50-60. 10.5740/jaoacint.SGE_Macfarlane

Maes, M., Kubera, M., & Leunis, J. C. (2008). The gut-brain barrier in major depression: intestinal mucosal dysfunction with an increased translocation of LPS from gram negative enterobacteria (leaky gut) plays a role in the inflammatory pathophysiology of depression. *Neuro Endocrinol Lett*, 29(1), 117-124.

Mawe, G. M., & Hoffman, J. M. (2013). Serotonin signalling in the gut-functions, dysfunctions and therapeutic targets. *Nat Rev Gastroenterol Hepatol*, 10, 473-486. 10.1038/nrgastro.2013.105

Matsumoto, M., Kibe, R., Ooga, T., Aiba, Y., Sakawi, E., Koga, Y., & Benno, Y. (2013). Cerebral low-molecular metabolites influenced by intestinal microbiota: A pilot study. *Front Syst Neurosci*, 7(9), 1-19. 10.3389/fnsys.2013.00009

Messaoudi, M., Lalonde, R., Violle, N., Javelot, H., Desor, D., Nejdi, A., & Cazaubiel, J.-M. (2011). Assessment of psychotropic-like properties of a probiotic formulation (*Lactobacillus helveticus* R0052 and *Bifidobacterium longum* R0175) in rats and human subjects. *Br J Nutr*, 105(5), 755-764. 10.1017/S0007114510004319

Miyake, S., Kim, S., Sada, W., Oshima, K., Nakamura, M., Matsuoka, T., Chihara, N., & Yamamura, T. (2015). Dysbiosis in the gut microbiota of patients with multiple sclerosis, with a striking depletion of species belonging to clostridia XIVA and IV clusters. *PLoS One*, 10(9), e0137429. 10.1371/journal.pone.0137429

Morowitz, M. J., Carlisle E. M., & Alverdy, J. C. (2011). Contributions of intestinal bacteria to nutrition and metabolism in the critically ill. *Surg Clin North Am*, 91(4), 771-785. 10.1016/j.suc.2011.05.001

Mouihate, A., Galic, M. A., Ellis, S. L., Spencer, S. J., Tsutsui S., & Spencer, S. J., Tsutsui S. (2013). Dysbiosis in the gut microbiota of patients with multiple sclerosis, with a striking depletion of species belonging to clostridia XIVA and IV clusters. *PLoS One*, 10(9), e0137429. 10.1371/journal.pone.0137429

Navarro, F., Liu, Y., & Rhoads, J. M. (2016). Can probiotics benefit children with autism spectrum disorders? *World J Gastroenterol*, 22(46), 10093-10102. 10.3748/wjg.v22.i46.10093

Nguyen, T. T., Kosciolek, T., Maldonado, Y., Daly, R. E., Martin, A. S., McDonald, D., & Jeste, D. V. (2019). Differences in gut microbiome composition between persons with chronic schizophrenia and healthy comparison subjects. *Schizophr Res*, 204, 23-29. 10.1016/j.schres.2018.09.014

Nishino, R., Mikami, K., Takahashi, H., Tomonaga, S., Furuse, M., Hiramoto, T., & Sudo, N. (2013). Commensal microbiota modulate murine behaviors in a strictly contamination-free environment confirmed by culture-based methods. *Neurogastroenterol Motil*, 25(6), 521-e371. 10.1111/nmm.12110

Ohland, C. L., Kish, L., Bell, H., Thiesen, A., Hotte, N., Pankiv, E., & Madsen, K. L. (2013). Effects of *Lactobacillus helveticus* on murine behavior are dependent on diet and genotype and correlate with alterations in the gut microbiome. *Psychoneuroendocrinology*, 38(9), 1738-1747. 10.1016/j.psyneuen.2013.02.008

Okubo, R., Koga, M., Katsunata, N., Odamaki, T., Matsuysama, Y., Oka, M., & Matsuoka, Y. Y. (2019). Effect of *Bifidobacterium breve* A-1 on anxiety and depressive symptoms in schizophrenia: A proof-of-concept study. *J Affect Disord*, 245, 377-385. 10.1016/j.jad.2018.11.011

Pierantozi, M., Pietroiuisti, A., Brusa, L., Galati, S., & Stefani, A., Lunardi...Galante, A. (2006). *Helicobacter pylori* eradication and L-dopa absorption in patients with PD and motor fluctuations. *Neurology*, 66(12), 1824-1829. 10.1212/01.wnl.0000221672.01272.ba

Peng, A., Qiu, X., Lai, W., Li, W., Zhang, L., Zha, X., & Chen, L. 2018. Altered composition of the gut microbiome in patients with drug-resistant epilepsy. *Epilepsia Res*, 147, 102-107. 10.1016/j.eplepsres.2018.09.013

Pereira, A. S. et al. (2018). Metodologia da pesquisa científica. UFSM. https://repositorio.ufsm.br/bitstream/handle/1/15824/Lie_Computacao_Metodologia-Pesquisa-Cientifica.pdf?sequence=1.

PRISMA (2015). Principais itens para relatar Revisões sistemáticas e Meta-análises: A recomendação PRISMA. *Epidemiologia e Serviços de Saúde*, 24(2), 335-342. Recuperado em 30 de março de 2021, de http://scielo.iec.gov.br/scielo.php?script=sci_arttext&pid=S1679-49742015000200017&lng=pt&tng=pt

Qin, J., Li, R., Raes, J., Arumugam, M., Burgdorf, K. S., Manichanh, C., & Wang, J. (2010). A human gut microbial gene catalogue established by metagenomic sequencing. *Nature*, 464, 59-65. 10.1038/nature08821

Scherperans, F., Aho, V., Pereira, P. A. B., Koskinen, K., Paulin, L., Pekkonen, E., & Auvinen, P. (2015). Gut microbiota are related to Parkinson’s disease and clinical phenotype. *Mov Disord*, 30(3), 350-358. 10.1002/mds.26069

Srikanta, P., & Hasan Mohajeri M. (2019). The possible role of the microbiota-gut-brain-axis in autism spectrum disorder. *Int J Mol Sci*, 20(9), 2115. 10.3390/ijms20092115

Stillings, 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, 99-110. 10.1016/j.neuint.2016.06.011

Tanouk, S. K., Regev, K., Healy, B. C., Cox, L. M., Tjon, E., Kivisakk, P., & Weiner, H. L. (2018). Investigation of probiotics in multiple sclerosis. *Mult Scler*, 24(1), 58-63. 10.1177/1352458517737390
Tamtaji, O. R., Heidari-soureshjani, R., Mirhosseini, N., Kouchaki, E., Bahmani, F., Aghadavod, E., & Asemi, Z. (2019b). Probiotic and selenium co-supplementation, and the effects on clinical, metabolic and genetic status in Alzheimer’s disease: A randomized, double-blind, controlled trial. *Clin Nutr*, 38(6), 2569-2575. 10.1016/j.clnu.2018.11.034

Tamtaji, O. R., Taghizadeh, M., Kakhaki, R. D., Kouchaki, E., Bahmani, F., Borzabadi, S., & Asemi, Z. (2019a). Clinical and metabolic response to probiotic administration in people with Parkinson’s disease: A randomized, double-blind, placebo-controlled trial. *Clin Nutr*, 38(3), 1051-1055. 10.1016/j.clnu.2018.05.018

Tomova, A., Husarova, V., Lakatosova, S., Bakos, J., Vlkova, B., & Ostatnikova, D. (2015). Gastrointestinal microbiota in children with autism in Slovakia. *Physiol Behav*, 138, 179-187. 10.1016/j.physbeh.2014.10.033

Turbaugh, P. J., Bäckhed, F., Fulton, L., & Gordon, J. I. (2008). Diet-induced obesity is linked to marked but reversible alterations in the mouse distal gut microbiome. *Cell Host Microbe*, 3(4), 213-223. 10.1016/j.chom.2008.02.015

Uher, R. (2014). Gene-environment interactions in severe mental illness. *Front Psychiatry*, 5(48), 1-9. 10.3389/fpsyt.2014.00048

Valverde, J. R., & Mellado, R. P. (2013). Analysis of metagenomic data containing high biodiversity levels. *PLoS One*, 8(3), e58118. 10.1371/journal.pone.0058118

Vetulani, J. (2013). Early maternal separation: A rodent model of depression and a prevailing human condition. *Pharmacol Reports*, 65(6). 10.1016/S1734-1140(13)71505-6

Vijay N, & Morris M. (2014). Role of monocarboxylate transporters in drug delivery to the brain. *Curr Pharm Des*, 20(10), 1487-1498. 10.2174/1381612813199990462

Vigo, D. V., Kestel, D., Pendakur, K., Thornicroft, G., & Atun R. (2019). Disease burden and government spending on mental, neurological, and substance use disorders, and self-harm: cross-sectional, ecological study of health system response in the Americas. *Lancet Public Heal*, 4(2), e89-e96. 10.1016/S2468-2667(18)30203-2

Yang, Z., Huang, S., Zou, D., Dong, D., He, X., Liu, N., & Huang, L. (2016). Metabolic shifts and structural changes in the gut microbiota upon branched-chain amino acid supplementation in middle-aged mice. *Amino Acids*, 48, 2731-2745. 10.1007/s00726-016-2308-y

Yano, J. M., Yu, K., Donaldson, G. P., & Shastri, G. G. (2015). Indigenous bacteria from the gut microbiota regulate host serotonin biosynthesis. *Cell*, 161(2), 264-276. 10.1016/j.cell.2015.02.047