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

Eixo cérebro-intestino e modulação imunoneuroendócrina em doenças neurológicas e psiquiátricas: Uma revisão sistemática

Eje intestino-cerebro y modulación inmune neuroendocrina en enfermedades neurológicas y psiquiátricas: Una revisión sistemática

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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-analyzes (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 the 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 neurossecretores; Doenças do sistema nervoso.

Resumen
El presente estudio tuvo como objetivo explorar la influencia del eje cerebro-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* y *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.

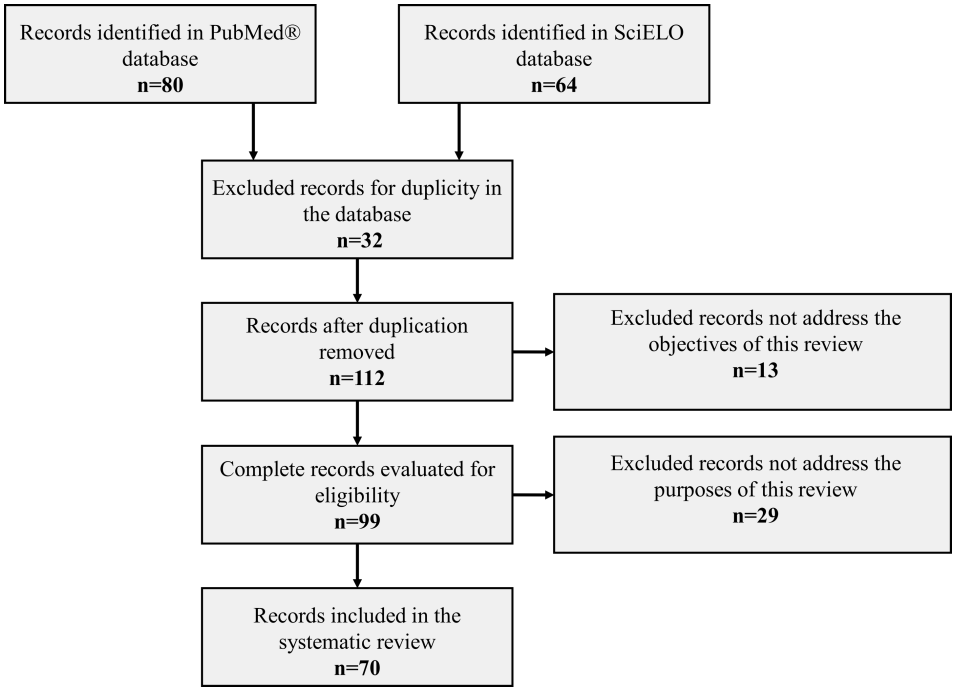
Animal and human model studies have been exploring the influence of the communication pathways between the gastrointestinal tract (GI) and the central nervous system (CNS), which make up the gut-brain axis, in the multi-causal picture of these disorders (Bravo, et al., 2011; Berer, et al., 2017). Several 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-analyzes – PRISMA (2015) guidelines and the procedures for the survey, selection and evaluation stages of the studies are illustrated in Figure 1.

Figure 1. Systematic review flowchart. PRISMA flowchart for paper selection for this systematic review.



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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.

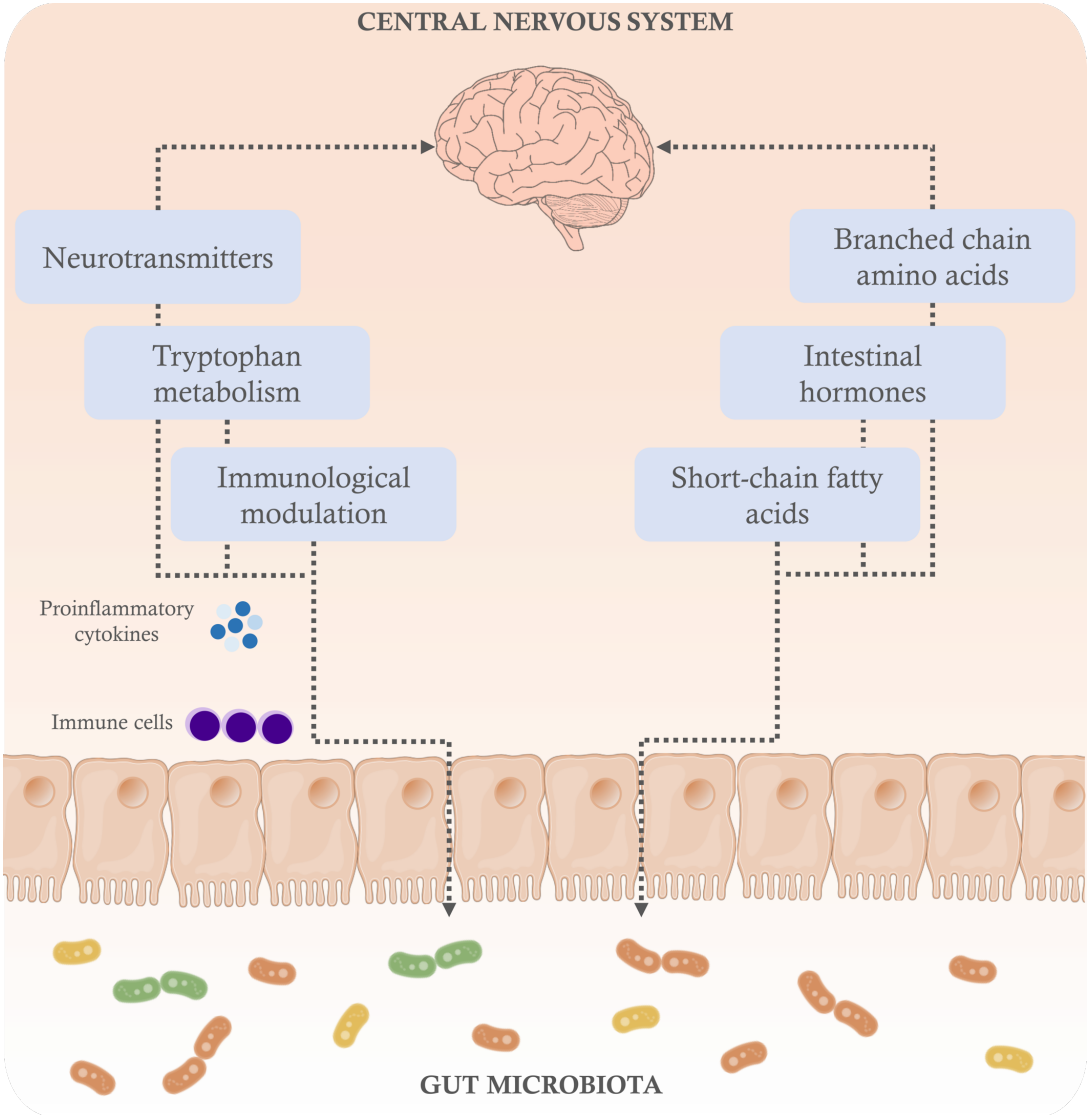
3. Results and Discussion

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.



Source: Authors.

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 and 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* *Streptococcus*	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 prausnitzii* 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				
Depression	Rats	*Bifidobacterium infantis* + citalopram	Decreased peripheral levels of cytokines and corticotrophin	Desbonnet, et al., 2010
	Rats	*Bifidobacterium animalis* subsp. *lactis*	Reversal of the exacerbated hypothalamic-pituitary-adrenal axis response	Barouei, et al., 2012
	Rats	*Lactobacillus farciminis*	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, succinite 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.

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