

Influence of gut microbiota on neuropsychiatric disorders

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Abstract

The last decade has witnessed a growing appreciation of the fundamental role played by an early assembly of a diverse and balanced gut microbiota and its subsequent maintenance for future health of the host. Gut microbiota is currently viewed as a key regulator of a fluent bidirectional dialogue between the gut and the brain (gut-brain axis). A number of preclinical studies have suggested that the microbiota and its genome (microbiome) may play a key role in neurodevelopmental and neurodegenerative disorders. Furthermore, alterations in the gut microbiota composition in humans have also been linked to a variety of neuropsychiatric conditions, including depression, autism and Parkinson's disease. However, it is not yet clear whether these changes in the microbiome are causally related to such diseases or are secondary effects thereof. In this respect, recent studies in animals have indicated that gut microbiota transplantation can transfer a behavioral phenotype, suggesting that the gut microbiota may be a modifiable factor modulating the development or pathogenesis of neuropsychiatric conditions. Further studies are warranted to establish whether or not the findings of preclinical animal experiments can be generalized to humans. Moreover, although different communication routes between the microbiota and brain have been identified, further studies must elucidate all the underlying mechanisms involved. Such research is expected to contribute to the design of strategies to modulate the gut microbiota and its functions with a view to improving mental health, and thus provide opportunities to improve the management of psychiatric diseases. Here, we review

the evidence supporting a role of the gut microbiota in neuropsychiatric disorders and the state of the art regarding the mechanisms underlying its contribution to mental illness and health. We also consider the stages of life where the gut microbiota is more susceptible to the effects of environmental stressors, and the possible microbiota-targeted intervention strategies that could improve health status and prevent psychiatric disorders in the near future.

Key words: Microbiota; Microbiome; Dysbiosis; Brain-gut axis; Mental health; Psychiatric conditions

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Core tip: The gut microbiota has been revealed as an additional regulator of the gut-brain axis, which may be involved in many neurodevelopmental and neurodegenerative disorders. The modulation of this axis is currently being explored, targeting the gut microbiota in endeavors to improve mental health, especially in early and late life. So far, most of our knowledge is based on animal trials, in which interventions with pro and prebiotics have shown promising results regarding efficacy. Nevertheless, we require further understanding of how the microbiota regulates gut-brain communication and function in order to establish the rationale behind microbiota-based interventions.

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INTRODUCTION

Research into the influence of human genetics on numerous conditions, including neuropsychiatric disorders, has been underway for many years; however, the etiology of most of these conditions has yet to be unraveled. As in other multifactorial conditions, there is considerable discordance in the development of neuropsychiatric disorders between monozygotic twins, indicating that non-genetic factors are also involved^[1,2]. Nowadays we know that both the human genome and the genome of the gut microbiota (microbiome) are essential for maintaining health, since the latter also plays a crucial role in regulating important aspects of host physiology, including brain development and function^[3,4]. Indeed, different studies have reported that gut microbiota is able to shape brain physiology and thus behavior through the gut-microbiota-brain axis and have suggested gut microbiota as a key trigger factor in the development of many neuropsychiatric conditions^[5].

Most of the neuropsychiatric disorders are considered as multifactorial disorders prompted by certain environmental factors in genetically susceptible individuals. However, there is a need of further work to elucidate the exact complex gene-environment interactions and gut microbiota alterations that precede the onset of the different neuropsychiatric diseases and their manifestations in order to decipher the etiology of the neuropsychiatric disorders.

It is noteworthy that the microbiota is more “medically” accessible and modifiable than the human genome. This fact provides a promising opportunity for preventing or treating neuropsychiatric conditions^[6]. In this respect, studies in animal models, where the intestinal microbiota can easily be manipulated, have shed light on how the microbiota may be involved in the development of certain mental diseases. In fact, different communication routes between the microbiota and brain have already been identified^[7] although further studies are required to elucidate the underlying mechanisms. Various studies also indicate that the activity of the gut microbiota can modify the host epigenome impacting on gene expression^[8]; furthermore, epigenetic mechanisms are involved in neurogenesis, neuronal plasticity, learning and memory, and in disorders such as depression, addiction, schizophrenia and cognitive dysfunction^[3]. Consequently, it has been suggested that gut microbiota may be involved in the pathogenesis and risk of developing neuropsychiatric disorders through epigenetic modifications, which are highly dynamic and reversible^[3]. Thus, it is tempting to speculate that modulating the microbiota and its metabolic products will enable us to modulate the epigenome and, thereby, prevent or treat mental illness. In this respect, metabolites produced by the microbiota from fiber fermentation are known to inhibit histone deacetylases (HDACs) and reduce inflammation through epigenetic modifications^[9].

Currently it is well accepted that our gut microbiota is critical for brain processes such as myelination, neurogenesis and microglial activation and can effectively modulate behavior and influence psychological processes such as mood and cognition^[10]. Indeed, very recently gut microbiota have been shown essential for the maintenance of microglia in a healthy functional state^[11], which is necessary for the prevention of neurodevelopmental and neurodegenerative disorders^[12].

The early assembly of a well-balanced microbiota composition and its subsequent maintenance is considered crucial for human health as perturbations negatively impact health and increase host susceptibility to a wide variety of diseases, including behavioral and neuropsychiatric disorders^[3,4]. In this respect, three critical time windows have been proposed including infancy, adolescence and ageing, when the gut microbiota is more vulnerable to external influence^[13]. Therefore, strategies aiming to target the

Table 1 Preclinical evidences of the role of gut microbiota on behavior

Germ-free (GF) mice have shown impaired social behavior ^[39]
GF mice have displayed exaggerated stress response ^[21] and differences in anxiety-like behavior ^[22,23]
GF mice have showed crucial changes in multiple neurotransmitters and their receptors in different brain regions ^[23]
GF animals have exhibited an impaired neurogenesis ^[25] and structural and functional changes in the amygdala ^[26]
GF mice have shown prefrontal cortical hypermyelination ^[27]
Microglial function impaired in GF animals is rescued by the oral treatment with short chain fatty acids ^[11]
Gut microbiota has been shown to modulate brain-derived neurotrophic factor, oxytocin and vasopressin brain levels ^[20]
Different probiotic preparations for administration to rats and mice have shown to achieve a reduction in anxiety-like and depressive-like behaviors ^[6,58]

gut microbiota might have a greater impact at those stages of life, *i.e.*, newborn, adolescence and elderly populations.

Many factors, including human genetics, influence the gut microbiota composition; therefore the microbiota constitutes a highly dynamic ecosystem, with high inter-individual variability^[14,15] and this indeed hampers the understanding of the role of gut microbiota in the etiology and progress of neuropsychiatric diseases.

Nowadays, each adult individual is believed to harbor a unique gut microbiota composition, as personal as a fingerprint, and certain early life events may be important contributors to the individual's microbiota, including mode of delivery, type of feeding, medication, stress and infections^[15]. The critical gut microbiota developmental period occurs in parallel to growth, maturation and sprouting of neurons in the young brain. In fact, childhood and adolescence represent the most dynamic and vulnerable periods for both gut microbiota composition and neuronal development^[16]. Furthermore, although the symbiotic link between the host and the microbiota seems to be established early in life, the gut microbiota composition may still experience changes in adulthood despite its greater resilience to the effect of detrimental environmental factors. Likewise, it is also well recognized that ageing is associated with reduced microbial diversity and that healthy ageing correlates with a diverse microbiota^[17]. Furthermore, research shows that as we age there is a decline in microbiota complexity parallel to a decrease in neuronal complexity and, altogether, those changes may lead to an increased risk of neurodegenerative disorders^[18]. Nowadays, it is well recognized that the onset of most of the neuropsychiatric disease really often is close to a period where the gut microbiota is more unstable and, therefore, at risk of suffering microbiota alterations. Despite these findings, there is currently a need for longitudinal studies in humans to assess the impact of the gut microbiota dynamics on the maintenance or decline of neurocognitive function and to understand to what extent results in animal models can be generalized to humans^[19].

In this review, first we summarize the current evidence for a role of the gut microbiota in brain development and function, and also summarize the state of the art on the different mechanisms involved.

Thereafter, we provide an update on research into specific neuropsychiatric disorders. We also refer to the different stages of gut microbiota development and maturation, identifying the periods where the gut microbiota is more unstable and, therefore, at greater risk of suffering microbiota alterations due to exposure to stressors. Lastly, we briefly highlight different microbiome intervention strategies that might be implemented to improve the management of psychiatric diseases.

MICROBIOTA, BRAIN DEVELOPMENT, FUNCTION AND BEHAVIOR

To investigate the role of the gut microbiota in the gut-brain axis, numerous approaches have been taken using animal models, including the study of microbiota deficient animals, known as germ-free (GF) mice, and of animals treated with antibiotics or with specific bacterial species. Such studies have provided new insights into how the microbiota is involved in regulating brain development and function (Table 1)^[20,21].

Recently, different studies using GF mice have demonstrated that animals completely lacking microbiota have impaired social behavior, as well as other types of behaviors such as anxiety and stress response^[22-24]. Furthermore, it has been observed that certain behaviors induced by the absence of gut microbiota correlate with neurochemical changes in the brain^[24]. Said studies have also shown crucial changes in multiple neurotransmitters and their receptors in different brain regions of GF mice. Moreover, the ability to transfer behavioral traits using fecal microbiota transplantation has also been demonstrated, suggesting that some microbiota changes could be rather a cause than a consequence of behavioral alterations^[25].

Recent data obtained using GF animals have shown that neurogenesis, a process that plays a critical role in modulating learning and memory, is also regulated by the microbiome^[26]. Furthermore, the gut microbiota is reported to modulate structural and functional changes in the amygdala, a critical brain area for social and fear-related behaviors, which are associated with a variety of neuropsychiatric disorders^[27].

Another aspect of neurodevelopment shown to be critically regulated by the microbiome is prefrontal cortical myelination^[28]. A recent study also showed that depletion of the gut microbiota as of early adolescence

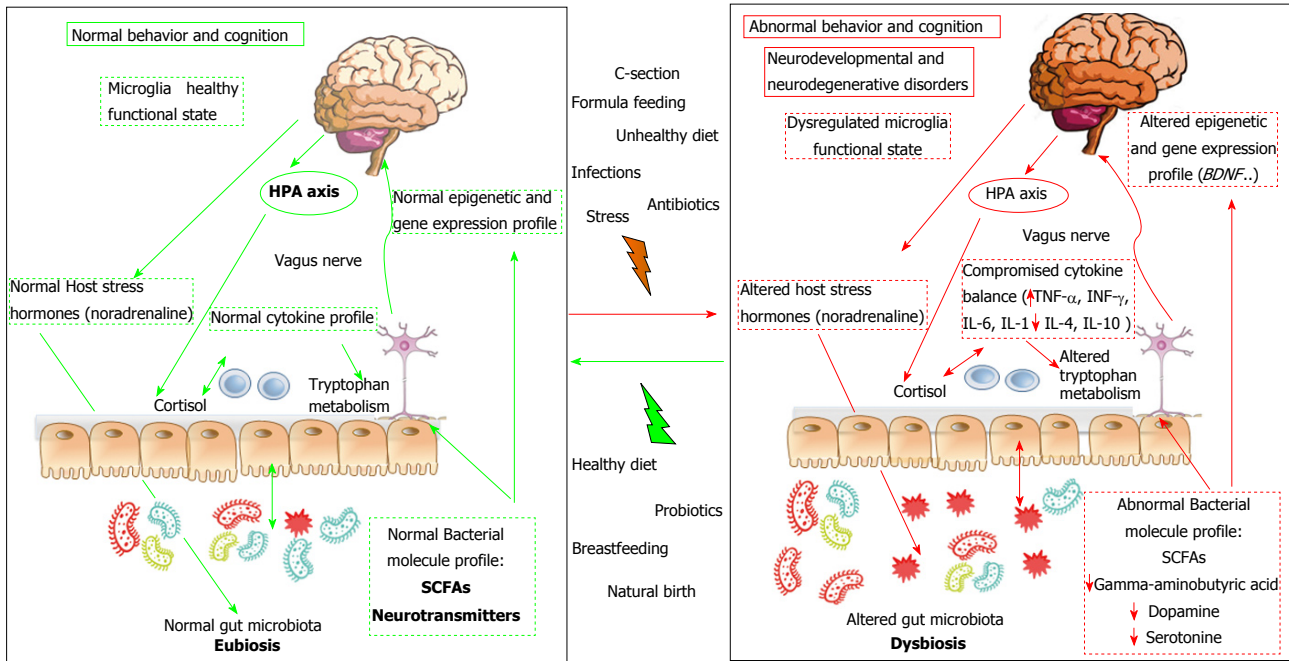


Figure 1 Schematic representation of the mechanisms involved in the relationship between microbiota and brain development and function: Cytokine balance and microglia activation (immune pathway), cortisol (endocrine pathway) and vagus and enteric nervous system (neural pathway). The axis plays an important role in homeostasis and has been linked to several disorders. Altered gut microbiota composition enhances the risk of neurodevelopmental and neurodegenerative disorders possibly from microbiota-derived products such as small chain fatty acids and neurotransmitters. HPA: Hypothalamic-pituitary-adrenal.

in mice alters their behavior and significantly reduces brain-derived neurotrophic factor (BDNF), oxytocin and vasopressin expression in the adult brain^[21].

Very recently it has been demonstrated that the maturation and activation of microglia, the macrophages of the brain crucial for maintaining brain tissue homeostasis, are also regulated by the gut microbiota^[11]. The same study demonstrated that treatment with microbial-produced short-chain fatty acids (SCFAs) could rescue microglial function impaired in GF animals^[11]. In addition, various studies have shown that probiotic administration to healthy rats and mice can alter behavior, achieving a reduction in anxiety-like and depressive-like behaviors and thus highlighting the beneficial effects of probiotics on stress-related behaviors^[6]. All these findings indicate that probiotics may have broader therapeutic applications than previously considered, particularly in the area of anxiety and depression^[6].

GUT MICROBIOTA MECHANISMS MODULATING BRAIN DEVELOPMENT AND FUNCTION

Recent studies have provided insights into the possible pathways and mechanisms that connect the microbiota to the brain. In fact, recent evidence largely suggests that there are several mechanisms by which microbiota may modulate brain development, function and behavior including immune (cytokines), endocrine (cortisol) and neural (vagus and enteric nervous system) pathways (Figure 1). Likewise, different mechanism

have been identified by which also brain can influence the gut microbiota composition^[7]. Results of animal studies show that stress and emotions cause the brain to influence the microbial composition of the gut through the release of hormones or neurotransmitters, which influence gut physiology and alter the habitat of the microbiota, resulting in preferential growth of certain communities. Indeed, host stress hormones such as noradrenaline might influence bacterial gene expression or signaling between bacteria, and this might change the microbial composition and activity of the microbiota. In addition, the microbiota has a substantial impact on the metabolomics profile of the host. It is important to highlight that a large array of crucial molecules with neuroactive functions is produced by microbes^[7]. Nowadays it is clear that certain bacteria are strain-specifically able to produce different essential neurotransmitters and specific neuromodulators. Indeed, several neurotransmitters such as gamma-aminobutyric acid (GABA), serotonin, catecholamines and acetylcholine are produced by bacteria, some of which are inhabitants of the human gut. Indeed, researchers report that *Lactobacillus* spp. and *Bifidobacterium* spp. produce GABA^[29]; *Escherichia* spp., *Bacillus* spp. and *Saccharomyces* spp. produce noradrenalin; *Candida* spp., *Streptococcus* spp., *Escherichia* spp. and *Enterococcus* spp. produce serotonin; *Bacillus* spp. produce dopamine; and *Lactobacillus* spp. produce acetylcholine^[6]. Neurotransmitters secreted from bacteria in the intestinal lumen may induce epithelial cells to release molecules that, in turn, have the ability to modulate neural signaling within the enteric nervous system

and subsequently control brain function and behavior. Various bacterial strains have also been shown to mediate behavioral effects *via* the vagus nerve in some animal studies although vagotomy does not seem to mediate all microbiota-mediated effects on brain function and behavior^[30].

Tryptophan is an essential amino acid precursor to many biologically active molecules, including the neurotransmitter serotonin and metabolites of the kynurenine pathway. Only around 5% of systemic tryptophan is metabolized into serotonin and the rest is metabolized along the kynurenine pathway. This depends on the expression of two enzymes, indoleamine 2,3-dioxygenase, which is found in all tissues, and tryptophan 2,3-dioxygenase, which is localized within the liver. The activity of both enzymes is strongly controlled by inflammatory mediators such as cytokines and corticosteroids. The increased activation of these two enzymes could induce serotonin depletion and depressive mood. Furthermore, the downstream metabolites of the kynurenine pathway are neuroactive metabolites, which can also modulate neurotransmission. In addition, the oral ingestion of *Bifidobacterium infantis* led to increased levels of the serotonin precursor, tryptophan, in the plasma of rats, suggesting that this specific strain may be a potential antidepressant. Other studies have also demonstrated the effect of the gut microbiota on the levels of other metabolites related with tryptophan metabolism^[31].

Other important molecules, which are produced in the colon by microbial fermentation of dietary fiber, are SCFAs such as butyrate, acetate and propionate. SCFAs are known to have neuroactive properties; for instance, the administration of a high dose of propionate in rats induced a neuroinflammatory response and behavioral alterations related with neurodevelopmental disorders^[32]. Propionate is also a common preservative in food products that has been demonstrated to exacerbate autism spectrum disorder symptomatology. Moreover, butyrate decreases depressive-like behavior with parallel changes in histone deacetylation and BDNF expression. SCFAs also regulate the gut immune system and this may have consequences on the central nervous system. As mentioned above, the maturation and activation of microglia is also regulated by the gut microbiota^[11] and oral treatment with microbial produced SCFAs can rescue microglial function impaired in GF animals^[11]. However, it is still unclear whether SCFAs produced in the gut can cross the blood-brain barrier.

EPIGENETICS, GUT MICROBIOTA AND NEUROLOGICAL CONDITIONS

It is currently well recognized that there are many changes in gene expression not caused by variations in sequence or genotype. Those changes are rather triggered by epigenetic modifications, such as methylation, acetylation or non-coding RNAs (ncRNAs),

which modulate chromatin remodeling and the final translation of coding mRNA into proteins. Several types of epigenetic-modifying enzymes together with ncRNAs are involved in epigenetic regulation and have been demonstrated highly sensitive to environmental changes. Therefore, epigenetic modifications associated to many diseases have been recognized as possible pieces missing in the puzzle linking the human genome, environment and phenotype development^[33]. Epigenetic mechanisms are currently known to be involved in neurogenesis, neuronal plasticity, learning and memory, and in disorders such as depression, addiction, schizophrenia and cognitive dysfunction^[3,34]. Many of the environmental factors apparently playing a crucial role in the etiology of neuropsychiatric disorders might be related with the risk of developing the condition through epigenetic mechanisms.

Changes in histone modifications and DNA methylation have been found at the promoters of genes involved in neuropsychiatric conditions^[3]. For instance, chromatin remodeling at the BDNF gene promoter has been associated with neuronal activity and stress and likely affects many more genes involved in brain function and behavior^[35]. In fact, there is now a great deal of evidence for the role of epigenetic regulation in shaping brain function and behavior, even though the underlying molecular mechanisms by which epigenetics might be leading to the behavioral and biochemical alterations observed in neuropsychiatric disorders are still not well understood^[36].

Gut microbiota has been shown to impact host gene expression by modulating epigenetic processes which are highly dynamic and reversible^[33]. Therefore, it is tempting to speculate that modulating the microbiota will enable us to shape our epigenome in the near future. Indeed, the methylation levels of specific genes involved in metabolism and inflammatory responses have been associated with gut microbiota profiles^[37]. Furthermore, various studies have described a link between microRNAs, a group of small ncRNAs, and microbiota^[38]. Histone deacetylations by HDACs are also critical in epigenomic regulation and are related with condensed chromatin and, consequently, the inhibition of the gene expression. Indeed, SCFAs have the capacity to inhibit HDACs, thus activating the gene expression of previously deacetylated genes^[33].

Aging is associated with profound epigenetic changes resulting in alterations in gene expression and also with a wide range of human disorders, including neurodegenerative diseases. Therefore, the reversibility of epigenetic changes that occur as a hallmark of aging offers exciting opportunities to treat age-related diseases^[39].

GUT MICROBIOTA AND NEUROPSYCHIATRIC CONDITIONS

So far many evidences derived from multiple studies performed in both animal models and humans have

Table 2 Current evidences linking gut microbiota to neuropsychiatric disorders

<p>Autism Increase in microbiota diversity is associated with autism^[43] Abundance of Bacteroidetes has found to be linked with severe autistic cases^[43] Increase in short chain fatty acids has been found in fecal samples from autistic children^[44] A specific strain of the species <i>Lactobacillus reuteri</i> has shown to modulate oxytocin levels and reverse autism-related behavior^[41]</p> <p>Schizophrenia Dopamine, the key neurotransmitter associated with schizophrenia pathophysiology, is produced by components of the microbiota^[53] Increased gastrointestinal inflammation is associated with schizophrenia^[53] Intake of antibiotics is associated with the risk of schizophrenia^[54]</p> <p>Attention deficit hyperactivity disorder The risk of developing ADHD has been suggested to be associated with many perinatal risk factors, including delivery mode, gestational age, type of feeding, maternal health and early life stressors, all of them linked to gut microbiota alterations^[56] Dietary components modulating gut microbiota may influence ADHD development or symptoms^[56]</p> <p>Depression Increase in gut microbiota alpha diversity is associated with depression^[59,63] Lower numbers of Bifidobacterium and Lactobacillus have been found in individuals with depression^[60] Increases in the genus <i>Eggerthella</i>, <i>Holdemania</i>, <i>Gelria</i>, <i>Turicibacter</i>, <i>Paraprevotella</i> and <i>Anaerofilum</i>, and reductions in <i>Prevotella</i> and <i>Dialister</i> have been found in individuals with depression^[61] A negative correlation between <i>Faecalibacterium</i> spp. and severity of depressive symptoms has been reported^[61] Role of diet on depression onset is suggested (Mediterranean diet seems to protect, whereas Western diet seems to be associated with an increased risk)^[64] Different strains of <i>Lactobacillus rhamnosus</i>, <i>Lactobacillus helveticus</i>, <i>Bifidobacterium longum</i>, <i>Bifidobacterium breve</i> and <i>Bifidobacterium infantis</i> have been shown to attenuate depression and anxiety-related behavior in rodents^[58] A probiotic combination (<i>Lactobacillus helveticus</i> R0052 and <i>Bifidobacterium longum</i> R0175) has proven effective in increasing the subject's resilience to stress in humans^[57]</p> <p>Parkinson's disease Alterations in bowel function, mainly constipation, often precede the onset of motor symptoms associated with PD^[76] Reduction in the levels of Prevotellaceae has been found in PD patients^[80] Positive correlation between levels of Enterobacteriaceae and the severity of postural instability and gait difficulty was proven in PD patients^[80] Reduction in short chain fatty acids^[78] and butyrate-producing bacteria (<i>Blautia</i>, <i>Coprococcus</i>, <i>Faecalibacterium</i> spp and <i>Roseburia</i>)^[79] were found in fecal samples from PD patients GF mice overexpressing human α-synuclein (αSyn) display reduced microglia activation, αSyn aggregates and motor deficits (treatment with short chain fatty acids restored all major features of PD in GF mice)^[77] Gut microbiota transfer from PD patients into GF mice overexpressing human α-synuclein (αSyn) enhances physical impairments whereas gut microbiota transfer from healthy human donor does not enhances those deficiencies^[77]</p> <p>Alzheimer's disease Risk factors for AD such as metabolic syndrome, type 2 diabetes and obesity are associated with gut microbiota alterations^[86,87] Gut microbiota seems to be involved in the accumulation of amyloid plaques according to the results of a study using a mouse model of AD^[88]</p>

AD: Alzheimer's disease; PD: Parkinson's disease; ADHD: Attention deficit hyperactivity disorder.

strongly suggested a link between gut microbiota and development and/or manifestation of different neuropsychiatric conditions (Table 2).

Microbiota and impairment of social behavior (autism), schizophrenia and attention deficit hyperactivity disorder

Studies using GF mice have demonstrated that animals completely lacking microbiota exhibit deficiencies in social behavior. In particular, John Cryan's research team examined the behavior of GF mice in the three-chamber test and observed that GF mice spent as much time with the familiar as with the novel mouse in contrast to the behavior of conventionally colonized mice, which spent more time with the novel than the familiar mouse^[40]. They also observed that GF mice spent longer with an object or an empty chamber than with another mouse, which is considered abnormal behavior for a sociable animal. Research has also demonstrated that colonization of the GF mice partially normalizes these behavioral impairments^[40].

Oxytocin is well known to influence social behavior^[41]

and evidence indicates that its levels are closely regulated by the gut microbiota^[42]. In fact, last year Desbonnet *et al.*^[21] showed that depletion of the gut microbiota as of early adolescence reduces oxytocin expression in the adult brain. Furthermore another recent study demonstrated that a single probiotic bacteria (a strain of the species *Lactobacillus reuteri*) can modulate oxytocin levels and reverse autism-related behavior, raising the possibility of influencing social behavior by targeting the gut microbiota^[42].

Autism spectrum disorder (ASD) is often associated with gastrointestinal co-morbidities and recent studies have shown changes in the gut microbiota of autistic children, including shifts in levels of Bacteroidetes and Firmicutes phyla with the abundance of Clostridium, establishing a strong link between gut microbiota and ASD^[43,44]. Research also reports an increase in microbiota diversity associated with autism in children with the abundance of Bacteroidetes found to be linked with severe autistic cases^[44]. Other gut commensals found to be altered in autism belong to *Bifidobacterium*, *Lactobacillus*, *Prevotella* and

Ruminococcus genera^[44] although these associations do not necessarily imply causality. In addition, a significant increase in SCFAs in fecal samples from autistic children has been recorded, providing a further indication for a role of an altered microbiota composition or function in this neurodevelopmental disorder^[45]. However, the role of SCFAs in ASD is not fully understood. For instance, administration of butyrate has been shown to improve repetitive symptoms in a murine model of ASD^[46] whereas intra cerebroventricular infusions of propionic acid induces autistic-like behaviors in rats^[47], thus suggesting SCFAs play differential roles in mediating ASD behavior. Therefore, further research is warranted to delve further into the role of SCFAs in autism.

In humans, prenatal exposure to the mood stabilizer valproate is a major risk-factor for autism^[48] and de Theije *et al.*^[49] have shown that the autism-like behavioral changes that occur in mouse models of valproate exposure are coincident with changes in microbiota composition.

In addition, maternal obesity is associated with neurodevelopmental disorders in offspring, including autism spectrum disorder^[50] and, in line with this observation, mice with induced obesity by a maternal high-fat diet (MHFD) show social behavioral deficits due to alterations in the gut microbiota^[51]. Buffington *et al.*^[51] recently observed that the diversity of the microbiota in MHFD offspring was reduced, showing a remarkable reduction in *Lactobacillus* spp. compared with the abundance found in the offspring of animals from mothers on a regular diet. Furthermore, it was demonstrated that treatment with a *Lactobacillus reuteri* strain not only augmented levels of oxytocin, improving social behavior, but also ameliorated synaptic dysfunction in MHFD offspring^[51].

Schizophrenia is another complex heterogeneous behavioral disorder characterized by abnormal social behavior, often associated with additional mental health problems such as anxiety disorders and major depression^[52]. To date the genomic analysis of schizophrenia has been limited, with the replicated genetic findings representing just a fraction of schizophrenia heritability^[53]. Furthermore, there is evidence for the important role that different environmental factors play in its development. In fact, several epigenetic mechanisms, in particular methylation of genes involved in neurotransmission, histone modifications and the action of ncRNAs, may also predispose individuals to schizophrenia. There are indications, such as the fact that dopamine, the key neurotransmitter associated with schizophrenia pathophysiology and treatment, is produced by microbes, and the increased gastrointestinal inflammation associated with schizophrenia, which strongly suggest that gut microbiota are involved in the risk of development schizophrenia or its manifestations^[54]. In addition, several studies have found an association between the intake of antibiotics and an increased incidence of

psychiatric disorders such as schizophrenia, perhaps due to alterations in the microbiota^[55]. However, to date there are not any published studies investigating the role of the gut microbiome in schizophrenia.

Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by inappropriate levels of hyperactivity, difficulty in controlling behavior and/or attention problems. Although ADHD is currently one of the most frequently studied disorders in children and adolescents, the exact mechanisms that predispose individuals are still unknown, though both genetic and environmental factors seem to be involved^[56]. Various factors associated with the risk of developing ADHD and/or linked to different ADHD manifestations have also been linked to shifts in gut microbiota composition, suggesting a link between the microbiota and the disorder. In addition, evidence from preliminary human studies suggests that dietary components modulating gut microbiota may also influence ADHD development or symptoms. Therefore, recently, after reviewing the literature, we argue^[57] that genomic studies in ADHD should include studies of the gut microbiota.

Microbiota, stress response and depression

Most organisms are equipped with biological machinery able to muster a defensive response to stressful stimuli. In response to stress, the hypothalamic-pituitary-adrenal (HPA) axis is activated and corticosterone releasing factor (CRF) is released from paraventricular neurons of the hypothalamus. CRF stimulates the release of adrenocorticotrophic hormone (ACTH) from the anterior pituitary, which in turn induces the synthesis and release of glucocorticoids from the adrenal cortex: cortisol in humans and corticosterone in animals. Studies in GF mice have revealed that the microbiota influences the development of the HPA axis and thus the stress response. Animals raised in a sterile environment from birth exhibit inflated HPA axis activity with elevated ACTH and corticosterone levels in response to a stressor^[22]. Interestingly, HPA axis activity is normalized after colonization with commensal bacteria from control mice^[25].

Although studies investigating the effects of prebiotic or probiotic supplements on stress behavior in humans are limited, they indicate the role of gastrointestinal microbiota in stress and emotional responses. Likewise, a probiotic combination (*Lactobacillus helveticus* R0052 and *Bifidobacterium longum* R0175)^[58] and a prebiotic (galactooligosaccharide)^[59] have proven effective in increasing the subject's resilience to stress and improved emotional responses in healthy subjects.

Depression is a stress-related mood disorder associated with a disrupted HPA axis, and evidence suggests that the gut microbiota play a key role in modulating depression^[60]. In fact, an increase in alpha diversity of the gut microbiota has been reported in individuals with depression compared to a healthy

control group. Furthermore, patients with depression show significantly lower numbers of *Bifidobacterium* and *Lactobacillus* compared to control subjects^[61]. In addition, a more recent study shows that patients with major depression have altered microbiota compared to normal subjects, with a significant increase in the genus *Eggerthella*, *Holdemania*, *Gelria*, *Turcibacter*, *Paraprevotella* and *Anaerofilm*, whereas reductions in *Prevotella* and *Dialister* were observed^[62]. Another recent study also reported a negative correlation between *Faecalibacterium* spp. and the severity of depressive symptoms^[62]. Moreover, researchers have demonstrated that when the microbiota from patients with major depression is transferred to microbiota-depleted animals, the behavioral and physiological features characteristic of depression are also transferred, supporting a link between dysbiotic microbiota and depression^[63]. A recent study published in *Science* reported a correlation between a more diverse gut microbiota composition and depression in humans after investigating the gut microbiomes of 1135 participants from a Dutch population cohort using deep sequencing^[64].

Different diets have been suggested to have either positive or negative effects on depression. For instance, a Western diet seems to be associated with an increased risk of depression, whereas the Mediterranean diet seems to reduce the onset of depression. Furthermore, studies in human and animal models have shown an association between depletion of omega-3 polyunsaturated fatty acids and major depression, suggesting the role of diet in depression onset^[65].

Different probiotic treatments have displayed efficacy in the reduction of depressive-like behaviors in animal models. For instance, administration of a probiotic cocktail comprising of *Lactobacillus rhamnosus* and *Lactobacillus helveticus* strains have been shown to ameliorate depressive-like behavior and normalize corticosterone levels in a maternal-separation animal model. Moreover, administration of *Lactobacillus rhamnosus* reduced depression and anxiety-related behavior. Also there is evidence for the association between different strains of the genus *Bifidobacterium* and potential antidepressant-like behavior in animals. Treatment with a strain of *Bifidobacterium infantis* attenuated depression, showing increased mobile episodes during the forced swim test in maternally separated rats. A similar effect was also observed with strains of *Bifidobacterium longum* and *Bifidobacterium breve* on depression and anxiety-related behavior in rodents^[60].

Gut microbiota and neurodegenerative conditions

Over a century ago, the Nobel Prize Elie Metchnikoff already suggested that the microbial communities within the gastrointestinal tract had an influence on human health. The Russian scientist Metchnikoff observed that people lived longer in parts of Bulgaria

and Eastern Europe because of the high consumption of fermented dairy products containing lactic acid bacteria, and suggested that complementing the diet with lactic acid bacteria would have health benefits, including longevity^[66]. The finding that germ-free mice live longer than their conventionalized controls was also reported many years ago^[67,68], supporting a link between microbiota and senescence. Nowadays, we know that the gut microbiota undergoes a dynamic change during aging^[69]. It is of interest that bifidobacteria numbers decrease with age, while those of clostridia increase^[70]. Age-related gut microbiota composition changes have also been correlated with health outcomes in the elderly, such as frailty^[71], with microbial diversity being an important feature linked to health maintenance as we age^[18]. However, major shifts in diet of the elderly could partly be responsible for the dramatic changes in microbiota composition and their association with health-related outcomes^[72]. This also suggests there is a chance of redressing the balance by dietary-based interventions in the elderly.

Aging can weaken gastrointestinal barrier function and promote a proinflammatory phenotype involving the microbiota^[73]. Another consequence of ageing is the progressive leakiness of the blood-brain-barrier (BBB), whose integrity also seems to be dependent on gut microbiota composition^[74]. SCFAs produced by gut microbiota components are considered key metabolites mediating such effects. Stress is one of the lifestyle factors that can negatively impact BBB permeability^[75] and accelerate the "inflamm-aging" processes linked to age-related diseases^[76]. Therefore, understanding how the gut microbiota or their components influence such processes is now worthy of attention.

Parkinson's disease (PD) is a neurodegenerative disorder that represents a growing health concern in the elderly. It is characterized by neuroinflammation and loss of midbrain dopaminergic neurons, as well as by a characteristic pattern of abnormal movements with a number of non-motor symptoms^[77]. It has also been observed that alterations in bowel function, mainly constipation, often precede the onset of prototypical motor symptoms associated with PD. While genetics plays an important role in the risk of developing the disease, environmental factors and gene-environment interactions also contribute to the risk for developing the disorder^[78]. In fact, evidence suggests that gut microbiota is an important environmental factor related to the risk of PD^[78-81].

Interestingly, a recent study sequenced the gut microbiota in patients with PD and controls^[81]. The authors of this study compared 72 patients and 72 matched controls, confirming a major reduction in the levels of Prevotellaceae in PD patients. They also observed and described a positive correlation between the levels of Enterobacteriaceae and the severity of postural instability and gait difficulty^[81], suggesting the role of the gut microbiota in the PD phenotype. Another study showed that at the taxonomic level of genus,

putative “anti-inflammatory” butyrate-producing bacteria from the genera *Blautia*, *Coproccoccus*, and *Roseburia* were significantly more abundant in feces of controls than PD patients. On the other side, in this study it was also reported that bacteria from the genus *Faecalibacterium* were significantly found more abundant in the mucosa of controls than PD patients, whereas putative “pro-inflammatory”. Proteobacteria of the genus *Ralstonia* were significantly more abundant in mucosa of PD patients than controls^[81].

Intriguingly, another recent study confirmed the recently reported association between PD and the reduced abundance of butyrate-producing bacteria, and also demonstrated a reduction in the relative SCFAs concentration in PD compared with the abundance observed in controls, suggesting a role for SCFAs in PD^[78]. However, prospective longitudinal studies in subjects at risk of PD are still required to further elucidate the causal role of the gut microbiota and microbial products in the development of PD and its manifestations.

Very recently it has been reported that gut microbiota is involved in motor deficits and neuroinflammation in a model of PD, suggesting that the changes in the gut microbiota represent a risk factor for PD^[78]. This study revealed that under GF conditions, or antibiotic-related bacterial depletion, transgenic animals overexpressing human α -synuclein (α Syn) (an abundant protein in the human brain involved in neurotransmitter release) displayed reduced microglia activation, α Syn aggregates and motor deficits (neuropathological features of PD) compared to animals with a complex microbiota. Conversely, they showed that treatment with SCFAs restored all major features of PD in GF mice. Furthermore, this study demonstrated that transplanting gut microbiota from PD patients into genetically susceptible mice (α Syn-overexpressing mice) enhances physical impairments when compared to microbiota transplant from healthy human donors^[78].

Alzheimer’s disease (AD) and vascular dementias are the most common causes of cognitive decline in ageing populations in Western countries^[82]. The deficit in synaptic plasticity is one of the many changes occurring with age. Specifically, the typical model of plasticity shows a reduction in the hippocampus long-term potentiation (LTP) of the middle-aged, but most dramatically in aging rats^[83]. A recent study has investigated whether the age-related deficit in LTP might be attenuated by changing the composition of intestinal microbiota with VSL#3, a probiotic mixture comprising 8 Gram-positive bacterial strains. The study showed that the age-related deficit in LTP was attenuated in VSL#3-treated aged rats and this was accompanied by a modest decrease in markers of microglial activation and an increase in expression of BDNF and synapsin^[84]. However, although these findings support the fact that intestinal microbiota can

be manipulated in order to positively impact neuronal function modulating microglial activation, at the moment we still need to be cautious and to investigate further the different probiotics that could be used to modify the microglial maturation and function.

Surprisingly, so far there is a lack of detailed analyses of the microbiota of patients with AD^[85]. However, in metabolic syndrome, type 2 diabetes and obesity, which are risk factors for AD^[86], there is an alteration in the gut microbiota^[87,88]. More recently, a research study using a mouse model of AD has implicated the microbiota in the accumulation of amyloid plaques^[89], and there is also evidence suggesting that gut microbiota might be directly linked to dementia pathogenesis by triggering metabolic diseases and low-grade inflammation^[90]. Different mechanisms may explain the link between gut microbiota alterations in obesity and T2D and the development of AD. For example, different studies have indicated that an altered gut microbiota linked to obesity increases intestinal permeability and contributes to systemic inflammation leading to insulin resistance and T2DM^[91]. In turn, insulin resistance and T2DM is a risk factor for development of AD. Furthermore, the vascular effects of obesity and T2D, related to changes on the gut microbiota, also appear to play an important role in the development of AD^[92]. A leading hypothesis on the pathophysiology of AD is the mis-metabolism of amyloid precursor protein. The A β peptide is derived from amyloid precursor protein by sequential cleavages of different proteases. The activity of these proteases involved in the generation of A β peptide is highly regulated by the inflammation, being the latter modulate as already mentioned by the gut microbiota. In fact, BACE1 enzyme is essential for the generation of β -amyloid and Interleukin 1 β , considered as a risk factor for AD development, has been observed to aggravate plaque formation by induction of BACE1 expression^[93].

However, although it has been suggested that alterations on gut microbiota observed in diabetes and obesity may be linked to the risk of developing AD, there is a need of further work to elucidate the specific gut’s microbes and the mechanisms involved in the link between obesity, T2D and AD.

Dysregulation of normal microglial functions such as synaptic pruning and regulation is increasingly found to be implicated in diseases associated with cognitive deficits^[12,94]. Microglia cells are also essential for clearance of debris, plaques and aggregates, thereby playing a fundamental role in neurodegenerative amyloid disorders, including Alzheimer’s, Huntington’s and Parkinson’s diseases, each associated with a distinct amyloid protein. Therefore, targeting dysregulated microglial functions represents a therapeutic opportunity for treating these disorders^[95,96]. Although the mechanisms that ultimately lead to neurodegeneration are different in each neurodegenerative disease, chronic inflammation that may be modulated by the gut

microbiota is typically a prominent feature in the progressive nature of neurodegeneration^[12].

CONCLUSION

It is becoming evident that brain development and function are dependent on the diversity and structure of the gut microbiota and may, therefore, influence mental health. This hypothesis is based mainly on animal trials and a few observational human studies associating gut microbiota alterations with mental disorders, including depression, autism and PD. This notion has been further supported by recent transplantation experiments where the gut microbiota has been shown to transfer a behavioral phenotype or the disease features to the recipient animal, providing stronger evidence for a causal relationship. However, longitudinal studies in humans are still needed to investigate whether the gut microbiota changes in subjects with different neuropsychiatric disorder can contribute to disease onset and the role of other interacting factors such as the diet. So far various communication routes between the microbiota and brain have been identified, including immune, endocrine and neural pathways. Thus, interventions with pro and pre-biotics in animal models have shown that the microbiota could play a role in mental health by regulating inflammatory and endocrine secretions, synthesizing neuroactive compounds and interacting with the vagal nerve. Greater understanding of the precise underlying mechanisms is required to develop a clear rationale for conducting microbiota-based interventions in humans. In particular, inflammation seems to be a critical pathophysiological feature of mental disorders and, therefore, a potential target for microbiota-based interventions. Nonetheless, further knowledge is needed on how microbiota signals generated in the gut can impact on microglial activation and neuroinflammation.

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