

Microbiota-Gut-Brain Axis and Mental Health

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ABSTRACT

Intestinal microbes seem to be direct mediators in psychopathology, although the exact relationship between microbiome/microbiota and psychism is unknown. This brief structured bibliographic review is quick secondary research conducted with the aim of synthetically compiling the clinically relevant information on this topic, taking into account that the qualified primary research published is limited, complex and heterogeneous. Non systematic search in several well qualified international academic bibliographic indexes obtaining n=80 references. Results revealed that host microbiota have multiple psycho-neuro-gastro-enterological implications via neuroendocrine, nervous and immune pathways. Microbiota also entail an essential impact on hippocampus-dependent learning and memory. Next, the relevant integration of genomics and metabolomics is highlighted so as to explain its possible causal effects on anxiety, depressive and other disorders, as well as the bidirectional implication of the entire vagus nerve in depression through the microbiota-gut-brain axis. Lastly, the possible favourable effects of interventions on such axis in order to improve mental health are mentioned. On the other hand, psychotropic drugs are increasingly used to treat functional gastrointestinal disorders. In conclusions, to modulate intestinal microbiota is a promising and useful therapeutic strategy for various mental, behavioural and neurodevelopmental disorders. It is important to coordinate relevant complementary medical care specialisations in this regard.

Keywords: Anxiety, Depression, Intestinal Microbiome, Intestinal Microbiota, Scoping review, Mental Health

INTRODUCTION

There is growing interest in the role of the gastrointestinal microbiota (the microbiota resides in several different parts of the body) [1] in maintaining mental health [2], the pathogenesis and development of mental, behavioural and neurodevelopmental disorders, as well as in several other complex host behaviours. In particular, gut microbes seem to be direct mediators in psychopathology, but the exact causal relationship between microbiota and psychism is not known. Improved understanding of biological sex differences in the microbiota may lead to advances in treating neurological and mental disorders, as well as increasing the potential for interventions in impending personalised or precision medicine [3].

This is a short, structured secondary research article that aims to address a complex, rather novel issue. The most recent, relevant information published in qualified scientific circles on the interrelationship of the gut-brain microbiota axis and possible related psychopathological

conditions will be explored, described and discussed in a comprehensive summary. Likewise, the possible pathogenic basis of the “metabolic organ” that is the microbiota for many neurological disorders of major health impact has been postulated for years [4,5]. They also influence other pathologies such as certain nephropathies, pre-eclampsia-eclampsia, systemic lupus erythematosus and several others – interrelationships that will not be discussed here.

MATERIAL AND METHODOLOGY

This contribution is a rapid scoping review [6] of the qualified scientific literature on a broad and general issue that is emerging relatively recently. The search strategy does not include protocols and is intended to be transparent and accessible from bibliographic repertoires and similar Internet crawling platforms. It draws on carefully selected primary and secondary, analytical and critical sources to identify the breadth and depth of the existing literature to establish the state of the art.

No attempt has been made to systematise this literature review, as the available scientific literature is complex and very heterogeneous. The presentation and analysis of the results will be limited to the findings of the selected research, prioritising those considered most relevant and recent, with the aim of achieving a reasonable degree of useful, up-to-date exhaustiveness. The searches, up until June 2023, were undertaken in several international electronic databases: a) using the descriptors “microbiota” plus “mental health” in all fields in PubMed (US National Library of Medicine, National Institute of Health), n= 1,329 references; b) using these descriptors in the title, abstract and keywords in Scilit Indexing (Scientific Literature), n= 836; c) in PsycINFO Journal (American Psychological Association), n= 2; and d) using “microbiota-gut-brain axis”, n= 4,956, n= 4,516, and n= 3, respectively, in the same repertoires. The Cochrane library returned n= 622 results with “microbiota” and “mental health” in the title, abstract or keywords, and n= 349 with “microbiota” and “depression”.

In addition to the articles found and selected, those articles that cite them, along with others related to those cited, have been added. Likewise added were those suggested in the numerous relevant secondary sources. Additionally, some books were added. So as to be operational the total number of references included has been limited to n= 80.

The main limitations of the study are the scarcity of primary sources of sufficient quality, as well as possible author bias in the final selection of papers. On the other hand, most of the results found were obtained from studies with too small a sample or with many other biases relating to inclusion, diagnosis, self-selection, abandonment, prevalence or incidence, etc. As an example, association, directionality and proven causality are often confused in research [7].

RESULTS AND DISCUSSION

Microbiota-Gut-Brain Axis

The microbiome is the microbial assemblage of bacteria, archaea (formerly archaebacteria, now considered independent beings), viruses that constitute the virome, fungi and protists (eukaryotic organisms), including their genes and metabolites, as well as the environmental conditions surrounding them in a particular biological niche [8]. The complicated gut microbiota ecosystem, formerly known as flora and now also as microbiome (which is rather the genetic expression of the microbiota), chemically transforms the components of the diet.

Available evidence suggests that gut microbiota is related to brain connectivity and cognitive performance [9].

The interplay between microbiota, nerve cells, immune cells and stem cells at the base of the intestinal crypts is intricate [10]. The microbiota-gut-brain axis has several types of well-established interconnections, mainly: 1) direct through the enteric nervous system and the vagus nerve; 2) direct through the lymphatic system (the gut and associated lymphoid tissue constitute the largest immune organ in the human body); 3) interconnection through immunomediators such as mast cells, which play an important role in many inflammatory reactions; 4) interconnection through the enteric microbiota and its metabolites; 5) and others [11].

Several neuroscientific studies have demonstrated the importance of the microbiota in the development of brain systems and their neurogastroenterological implications. The gut-brain axis plays an important role in maintaining immune, metabolic and tissue homeostasis in the gut, as well as in the central nervous system. The nature of their bidirectional interrelationship with the healthy and dysfunctional brain through neuroendocrine, nervous and immune signalling pathways is, however, unclear. The microbiota is also involved in synthesising several neurotransmitters such as serotonin, norepinephrine and dopamine, which are involved in modulating gastrointestinal secretion and peristalsis, as well as in the subject's behaviour. This also influences the plasma levels of brain-derived neurotrophic factor (BDNF). Digestive or functional gastrointestinal disorders, now recognised as disorders of the gut-brain interaction, account for at least 40% of all consultations with gastroenterologists. They can affect any segment of the digestive tract. Although its aetiology is largely unknown, immune activation following antigen presentation in the intestinal mucosa may be a major cause of many clinical symptoms [12]. Metagenomic studies using next-generation sequencing technologies efficiently contribute to understanding the composition of the microbiota and its interaction with the brain [13,14].

The digestive system was described in 1999 by M. Gershon as the “second brain” [15]. Today, so-called irritable bowel syndrome (IBS) is classified as a functional gastrointestinal disorder in the corresponding chapter of the ICD-11 for Mortality and Morbidity Statistics (MMS). In this syndrome, the nerves responsible for peristalsis are sensitised. It is different from inflammatory bowel diseases such as Crohn's disease or ulcerative colitis, which are states of chronic intestinal inflammation of similarly uncertain aetiologies.

Irritable bowel syndrome symptoms are persistent or recurrent, with no underlying cause or structural abnormalities in the intestinal tissue identified, and it is therefore considered an idiopathic functional disorder [16]. The presence of abdominal pain seems essential [17]. In the past, this syndrome was also called colitis, mucous colitis, spastic colon, nervous colon, spastic bowel, functional dyspepsia, etc.

When constipation predominates in patients with irritable bowel syndrome, the corresponding formal clinical practice guideline can be applied, according to the latest systematised Rome IV criteria [18–20]. These current criteria emphasise the biological-psycho-social model. If diarrhoea predominates, more than a quarter of the stools will be loose or liquid. Of course, among other pathologies, giardiasis, caused by the protozoan parasite *Giardia lamblia* and a

major cause of diarrhoea, must be ruled out. A mixed or indeterminate syndrome may also occur.

It has been known for years that changes in the microbiota, which persists throughout the life cycle and whose individual composition is unique, are an underlying factor in the overall symptomatic perpetuation of IBS [21]. It is now added that the gut microbiota has a substantial impact on hippocampus-dependent learning and memory in rodents (the strongest evidence for the role of microbes in the gut-brain axis comes from animal studies) through several closely integrated major pathways [22]. In humans, associations between composition and diversity mediate the temperament of young children [23]. Indeed, gut microbes directly and indirectly influence the tryptophan metabolism, with corresponding changes in behaviour and cognition [24].

Functional gastrointestinal disorders are often found: 1) dysbiosis or dysbacteriosis, as it is well known that the digestive system and the brain's perception of stress are interrelated. Compositional and functional alterations in the gut microbiota have been reported in patients with stress-related mental and behavioural disorders. The dysbiotic microbiota is implicated in the pathogenesis of depression and, at the same time, offers a new therapeutic target [25]; 2) alteration of mucosal immune function; 3) visceral hypersensitivity; and 4) abnormal gastrointestinal motility [26,27].

In particular, and as a link to the following section, the presence of clinical depression in patients with ulcerative colitis appears to show significant differences in the composition of the gut microbiota compared to patients with ulcerative colitis without depression [28].

Relationship with Psychopathology, Especially Anxious-Depressive Psychopathology

The gut microbiota is known to produce a large number of metabolites that can be transported to the host and play a role in the homeostatic control of metabolism as well as in brain function [29]. A comprehensive multi-omics network related to depression and anxiety in active ulcerative colitis has just been identified. The involvement of the microbiota in gut disorders co-existing with neuropsychiatric disorders has also been highlighted [30]. The nomothetic “network theory” or general principles on symptoms, which at present remains merely hypothetical or unproven, purports to conceptualise mental disorders as symptom networks and treatments as interventions that seek to change them [31,32].

Despite the insufficient power of the studies due to small pilot sample sizes, potential associations between microbiota and early cognitive development measurements have been identified [23,33]. Exposure to adversity in the prenatal and postnatal period impacts the gut microbiome and is associated with an increased risk of psychopathology, which can be perpetuated across generations [34,35]. With the technologies available for molecular analysis and diagnostics, multi-omics networks allow the simultaneous detection of gene expression profiles and proteins [36]. These putative networks make it possible to complete the genetic diagnosis and increase the favouring study of the relationship between diet, gut microbiota and mental health.

Through the integration of genomics and metabolomics (the latter reflecting the net effect of genetic and environmental influences), the causal effects of genetically determined metabolites

and gut microbiota biosynthetic genes on anxiety disorders have been identified [37,38]. The first systematic reviews of the relationship of the microbiota specifically to these latter disorders [39], and also to mental, behavioural and neurodevelopmental disorders as a whole, have now been published [40].

The gut microbiota appears to be different in patients with social anxiety disorder compared to controls [41]. Similarly, in mice, it seems well established that the microbiota influences stress-related systems and in particular anxiety-like behaviour as assessed in multiple experiments [42] through the miR-206-3p/Cited2/STK39 axis [43]. Furthermore, dysbiosis and various gut microbiota, especially Firmicutes and Bacteroidetes, also appear to be shown to affect mental health via the microbiota-gut-brain axis [44].

With regard to the risk of clinical depression, the effects of gut microbiota-inflammatory disease interactions have been supported and several novel candidate genes for depressive disorders have been reported [45]. Increased prevalence of depression has been observed in younger patients with combined inflammatory bowel disease and rheumatoid arthritis, the latter two being immune-mediated inflammatory conditions [46]. The imbalance of the microbiota-gut-brain axis also leads to dysregulation of the hypothalamic-pituitary-adrenal axis, which is fundamental in the pathogenesis of depression [47].

The incidence of IBS is higher in women and there is in any case a very likely association with mental, behavioural and neurodevelopmental disorders. Multiple factors are responsible for triggering and perpetuating the syndrome, and in particular there is overlap in the common pathways for the syndrome and depressive disorders [48]. For their part, the precise mechanisms underlying the pathophysiology of depression remain elusive, although they are accompanied by low-grade activation of the immune-inflammatory response system. In psychiatric research in recent years, the functions of the immune system and the correlation of neuroinflammatory processes with mental disorders are of considerable importance [49].

It has been suggested that the vagus nerve, which as noted in the previous section is responsible for facilitating communication between the brain and gut, influences depression via the microbiota-gut-brain axis pathway [50]. Elongation of the left cerebral cross-section of the vagus in patients with depressive disorders, especially if they suffer from recurrent depression, could become a promising imaging biomarker [51]. In any case, it appears that the integrity of the vagus is required to induce persistent deficits in adult hippocampal neurogenesis and to elicit early and sustained neuroinflammatory responses in the adult hippocampus [52].

Mental, behavioural and neurodevelopmental disorders are more common in patients with inflammatory bowel disease than in the general population. Women with these pathologies are more likely than men to develop affective disorders and up to 65% will suffer from depressive and anxiety disorders [53]. In general, in functional digestive disorders, the most common neuropsychiatric comorbidities are, in addition to those mentioned above, Parkinson's disease and autism spectrum disorders [32,54,55]. In particular, preliminary data show that microbiota-based therapies have a positive effect on patients on this spectrum [56]. Neurodegenerative disorders may also be related to the immune-intestine-brain system [57]. Epigenetic changes such as deoxyribonucleic acid (DNA) methylation, histone modifications and ribonucleic acid (RNA) interference can influence gene expression and cause neuronal

alterations characteristic of many mental and behavioural disorders. Age and chronic stress, which is capable of triggering or reinforcing certain neural pathways, affect the levels of hippocampal monoamine receptor messenger RNA. These changes are correlated to altered behaviours in younger female mice, but not older ones [58].

There are similar microbial alterations in depressive, bipolar, anxiety and psychosis disorders, all characterised by a decrease in anti-inflammatory bacteria producing butyrate, a crucial metabolite of short-chain fatty acids, as well as an enrichment of pro-inflammatory bacteria [59]. In line with what has been said so far, diagnosis and coordination between different and complementary levels of care will often be needed.

Foreseeable Therapeutic Implications for Mental Health

A number of studies point to the encouraging implications of optimising the treatment of clinical depression by personalising the gut microbiota, but these have yet to be confirmed in humans. Combining the administration of selective serotonin reuptake inhibitors with probiotics containing specific bacteria has been shown to be beneficial [60]. Note that the gut microbiota can influence the metabolism of antidepressants to change their availability and regulate their absorption by affecting intestinal permeability [61].

So as to assess the therapeutic options properly, it would be necessary to establish what might be called an individual's "stool signature" [62], close to the individual phenotype information. The probiotic bacteria *Bacillus clausii* and *Lactobacillus fermentum* NMCC-14 may be particularly favourable in combating perceived excess stress and other psychiatric-neurological disorders [63]. Even in 2020, the bacterium *Christensenella minuta*, present in the gut of healthy individuals, was patented with the claim to prevent mood disorders.

It is also worth noting that research has illustrated in animals the usefulness of treatment with faecal microbiota transplantation [64]. In people, such transplantation can increase the proportion of those with active ulcerative colitis who achieve clinical and endoscopic remission [65]. Transplantation refers to the introduction of intestinal microbiota from the faeces of a healthy donor into the gastrointestinal tract of the patient. It has also been suggested that vitamins derived from the gut microbiota may contribute to mental health and treatment of related pathologies [66]. Some underlying mechanisms involved in mediating the influence of gut microbiota and probiotics on mental health through epigenetic modifications have already been elucidated [67].

As outlined in the previous section, the environmental factors that act epigenetically to influence the pathogenesis of mental and behavioural disorders are: social, high prenatal maternal stress, poverty, migration, urban housing, complications of pregnancy and childbirth, alcohol and substance abuse, microbiota, and prenatal and postnatal infections [68,69]. Naturally, this would only be the case if there is a personal lack of adequate adaptation to perceived stress, [70], or inability to successfully modify the stressor.

Neuromodulators such as antidepressants, antipsychotics and other drugs targeting the central nervous system are increasingly used to treat functional gastrointestinal disorders. Guidelines for such treatments have even been established [71]. Integrated care models have proposed best practice recommendations, including dietary and behavioural interventions to positively

influence these prevalent gastrointestinal pathologies [72]. On the other hand, focusing on the microbiota and the non-essential amino acid proline in the diet could open new windows for more effective treatment of clinical depression [73].

The favourable use of acupuncture techniques in functional digestive disorders has also been proposed, although without clear empirical evidence. Acupuncture as a purported therapy faces significant methodological challenges, although its regulatory effect on the immune system has gradually been recognised [74]. These techniques, apart from pharmacotherapies and psychotherapies, are popularly considered “treatments” [75], which, if prescribed by non-medical personnel, could eventually amount to professional intrusion with respect to the competent specialisations. This does not preclude that, as a favourable example in another field, acupuncture can improve recovery in patients with spinal fusion surgery [76].

Something similar can be said of the recommendation to practice full awareness or mindfulness, which has been widely studied in the West to reduce psychic distress, whether pathological or not [77,78]. In particular, mindfulness practice aimed at relieving maternal psychological distress can positively alter the microbiota of infants’ meconium [79]. And mindfulness-based cognitive therapy promotes similarity of the gut microbiota of people with high trait anxiety compared to healthy controls [80]. Overall, reasonable therapeutic caution should be exercised with regard to incessant proposals for “alternative”, integrative or collaborative intervention strategies.

CONCLUSIONS

In accordance with the demands for accuracy and objectivity that are inherent in science methodology, from the perspective of health and despite the numerous gaps in information, this contribution’s main conclusion is to emphasise that it is appropriate to bear in mind the bidirectional relationship of the microbiota-gut-brain axis with possible, even probable related psychopathology. Apart from the possibility that science mythologises reality, which is typical of extreme scientism, and its mystification by pseudo-sciences, the psychobiological basis and interrelation of most mental, behavioural and neurodevelopmental disorders is an undeniable fact.

Increasing importance is being placed on the gut microbiota/microbiome as it plays a facilitating role in the response to stress, inflammation, depression and anxiety. Thus, modulating the gut microbiota, mainly through diet and improved stress management (which has the capacity to deregulate gut bacterial composition), may be a promising therapeutic strategy for various mental, behavioural and neurodevelopmental disorders.

In this brief, narrative and simplified scoping literature review, the priority has been to collect information on the bidirectional relationship of gut microbiota, immune system and neuroinflammatory processes with anxiety and depressive disorders, which may also be influenced by gender. The potential therapeutic connotations for mental health of interventions on the gut-brain microbiota axis have also been broadly addressed.

Medical knowledge is necessarily profound, biological and psychosocial. As a logical corollary in the field of mental health, diagnosis and coordination between the corresponding complementary medical care specialisations should be more common and commonplace, as

well as non-intrusive collaboration with various beneficial non-health interventions such as diet, physical exercise, acupuncture, mindfulness, so-called “art therapy” and others.

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