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Can microbiology affect psychiatry? A link between gut microbiota and psychiatric disorders

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Summary

Every single human consists of thousands of genes, billions of neurons and trillions of bacteria. There is a rapidly growing number of data that links the gut microbiome to the development and functioning of the central nervous system, which is a currently proposed paradigm shift in neuroscience. Knowledge on the relationship between gut microbiota and mental disorders is constantly increasing. This phenomenon is known as "gut-brain axis". The strongest evidence for the role of microbes in the gut-brain axis comes from animal studies. Nevertheless, the gut-brain crosstalk is a bidirectional communication system that not only provides gastrointestinal homeostasis, but can also affect motivation as well as higher cognitive functions. Moreover, gut microbiome can be associated with obesity and inflammatory gastrointestinal disorders. According to the recent studies, there is a link between the composition of gut microbiota and mental disorders in animals (response to depression and chronic stress). This subject requires further examination, especially taking into consideration potential therapeutic options.

Key words: gut microbiota, gut-brain axis, mental health

Introduction

An amazing progress in knowledge of the influence of the intestinal microbiota on brain functioning, behavior and mental health has been observed for the last 5 years []. What is more, the intestinal microbiota may be associated not only with gastrointestinal disorders [2–6], such as inflammatory bowel disease [7], but also with neuropsychiatric disorders such as: depression [8–10], anxiety [8, 11], autism [12], anorexia [13], or even Alzheimer's disease [14, 15] and Parkinson's disease [16]. Correlation between the gut microbiota and attention deficit hyperactivity disorder (ADHD) was shown in

another study [17]. More than 4,000 articles on microbiota were published in PubMed and over 90% of them between 2010 and 2015 [18]. The term "microbiome" refers to all organisms and genetic material that are present in the human body, in contrast to the term "microbiota" that refers to populations of microorganisms present in various body ecosystems, such as gut microbiota [19]. In 2012, it was estimated that there are 10^{14} microorganisms in the human intestines, which is 10-fold more than the number of human cells. Moreover, the genome of the human gut microbiota was estimated to contain 3.3 million of microbial genes, which is circa 150-fold more genes than in the human genome [20, 21]. In 2016, Sender et al. [22] verified these data and estimated that in the upper small intestine (duodenum and jejunum) exist 10^3–10^4 microorganisms, in the lower small intestine (ileum) – circa 10^8 microorganisms, whereas in the colon – 10^{11}. Various bacterial families, such as *Firmicutes*, *Bacteroidetes*, *Actinobacteria* and *Proteobacteria*, reside in the human intestines [19]. The human gut microbiota consists of more than 1,000 species and over 7,000 subspecies of microorganisms [21].

In 1989, the hygiene hypothesis was originated [23]. According to this hypothesis, *Homo sapiens* had been evolving and co-living with friendly microorganisms in their bodies for thousands of years. Rook et al. [24] extended this thesis by stating that interactions between the gut microbiota and its host depend on the metabolites and nucleic acids produced by microorganisms. Those substances are transported into the human systemic circulation and can induce activation of inactive genes via epigenetic mechanisms, which finally contributes to evolution, but can also result in the development of various diseases [25, 26]. Shared endocrine signaling between bacteria and the host is an interaction of microbiology with the endocrine system of the host, which is called microbial endocrinology [2]. Gut microbiota can influence central nervous system (CNS) functions due to its ability to synthesize or mimic a wide range of neuroactive molecules [27] and this relation seems bidirectional. Examples of such molecules (as cited in: Petra et al. [17] and Barret et al. [27]) are presented in Figure 1.

According to Iyer et al. [28], microbiota uses exactly the same biochemical pathways to produce neurotransmitters as its host. It has been proposed, that the development of those biochemical pathways occurred in bacteria and by late horizontal gene transfer they were acquired by the eukaryotic cell system.

The Human Microbiome Project (HMP), that is being currently conducted, is similar to the Human Genome Project and its aim is to examine the diversity of microbiome and microbiota in various anatomical regions and to determine the role of microorganisms in health and disease [29, 30]. According to the results of research recently conducted in the Human Microbiome Project, bacterial-mammalian cell lateral gene transfer of bacterial DNA into human somatic genome occurs via integration of RNA and is more common than previously expected [31].

A link between the gut and the brain, which is established during intrauterine period, may be influenced by a lot of factors, including: antimicrobial treatments, vaccinations, intensive use of disinfecting and cleaning products, and dietary changes [18]. Moreover,

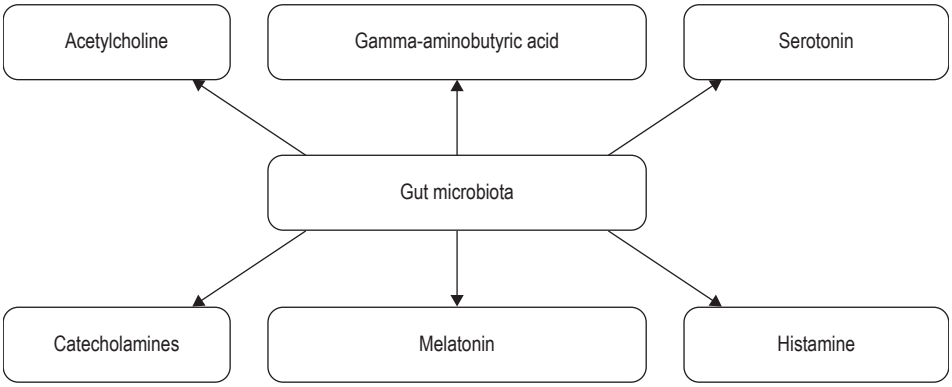

Figure 1. **Neuroactive molecules synthesized or mimicked by gut microbiota (own elaboration)**

our microbiome may be modulated by numerous other circumstances, such as: the mode of delivery (vaginal or C-section), the mode of feeding in the early infancy, exposure to viral or bacterial infections or stress [32]. Moreover, the development of intestinal bacteria occurs in parallel with the growth and maturation of neurons in the brain [32, 33]. Genes involved in formation of the synapses between neurons in the brain and neurons in the gastrointestinal (GI) tract are relatively similar and any mutations could possibly lead to both brain and GI abnormalities [34]. Theoharides et al. [35] described transcriptome changes, such as down-regulation of genes involved in mitochondrial function and ATP production, and up-regulation of genes involved in inflammation and dysfunction of genes involved in oligodendrocyte activities, in patients with autism, bipolar disorder, severe depressive disorder, schizophrenia, and multiple sclerosis.

The effect of the gut microbiota on human health is assumed to be an area of a great interest in neurobiology in the following years. It is even suggested that the microorganisms can be a new group of drugs named "psychomicrobiotics" applied among others in psychiatry [36].

To illustrate the importance of a proper regulation of gut microbiota, for example by using diet, probiotics and FMT, health consequences of changes in composition of the gut microbiota have been presented in Table 1 [37–45].

Table 1. **Correlation between changes in composition of the gut microbiota and diseases that can be associated with them (own elaboration)**

Gastrointestinal disorders	Non-gastrointestinal disorders
– inflammatory-mediated diseases in the gut [2, 7]	– allergic diseases (especially food allergies) [38–40]
– obesity and metabolic disorders [2–6]	– autoimmune diseases [38, 41]
– functional gastrointestinal disorders [37]	– anxiety disorder [8, 11]
	– depression [8–10]

table continued on the next page

	– Alzheimer's disease [14, 15]
	– Parkinson's disease [16]
	– multiple sclerosis [42]
	– mood disorders [17]

Development and maturing of intestinal microbiota

The composition of intestinal microbiota in children younger than three years old is different from that present in adults. The development of intestinal microbiota can be classically divided into two stages – the first stage with relatively anaerobic bacteria, such as *Escherichia coli* and other Gramm (-) bacteria from *Enterobacteriaceae* and *Enterococcus* and second stage when the above-mentioned bacteria exploit oxygen supply and the intestinal environment becomes anaerobic and expansion of strictly anaerobic bacteria, such as *Bifidobacterium*, *Clostridium*, *Bacteroides* and *Ruminococcus* is promoted [46]. Gut microbiota composition of the individual depends on several factors, such as: mode of delivery, genetic predispositions, age, nutrition, environmental factors, stress, infections, other diseases, and use of antibiotics [17]. Children with vaginal delivery maintain dominance of *Lactobacillus*, *Bifidobacterium*, *Prevotella*, and *Sneathia* – the bacteria that reside in both digestive and genital tract of their mothers. In comparison, children born by C-section maintain dominance of *Staphylococcus*, *Corynebacterium* and *Propionibacterium* – the skin microbiota of their mothers [47]. In infants with C-section delivery, the colonization of the digestive tract by *Lactobacillus* occurs 10 days after birth and by *Bifidobacterium* after the end of the first month of life and can be even delayed to the sixth month of life [48–50].

The data on the influence of probiotic supplementation during gestation and lactation are ambiguous. Penders et al. [51] indicated that the use of antibiotics and probiotics by pregnant women had no influence on intestinal microbiota of their babies. On the other hand, Fallani et al. [52] proved that antibiotic therapy during pregnancy lead to increase in the amount of commensal bacteria in stool samples and a lower proportion between *Bacteroides* and *Atopobium* in their children, in comparison to babies of women without antibiotic therapy.

Composition of intestinal microbiota is not constant during lifetime. It alters throughout the life of the individual due to various factors and in parallel with changes in the nervous system.

The role of microbiota in the development of the nervous system

Maternal health plays a key role in the development of microbiota as well as in the neurodevelopment [53]. Neurodevelopment and concurrent development of intestinal

microbiota can be influenced by numerous external and internal factors – maternal diet, prenatal stress, infections during the prenatal period. These factors may be associated with neurodevelopmental disorders, such as autism, ADHD or schizophrenia [54–57].,Thus, characterizing the composition of microbiota during pregnancy and its contribution to the neurodevelopment of the newborn seems to be an important step in developing microbiota-modulating interventions in humans. As mentioned above, the development of intestinal bacteria coexists with the growth and maturation of neurons in the brain [32, 33].

The shaping of intestinal microbiota occurs simultaneously with neurodevelopment and both the processes have similar critical developmental windows, with the highest sensitivity to damage. Early adolescence is a key stage and represents a high level of vulnerability to pathological factors. Moreover, adolescence is also the peak time for the onset of numerous psychiatric diseases, such as schizophrenia, substance abuse and mood disorders [58].

In conclusion, the vulnerability of the brain of the adolescent to pathological factors, such as stress, substances, poor diet in combination with instability and immaturity of the gut microbiota makes the brain susceptible to both development and occurrence of diseases or disorders in this period of life [32]. The qualitative composition of intestinal microbiota and its stability decline with aging [59, 60]. Aging may have negative impact on gut microbiota, which may influence health at this stage of life [61]. Thus, maintaining a healthy gut microbiota and mental health seems an important factor in preventing brain disorders connected with ageing [32].

Gut-brain axis – a connection between microbiology and psychiatry

The intestinal microbiota can bidirectionally communicate with the central nervous system via numerous mechanisms: changes in microbial content [62], immune stimulation [18], through neural pathways (the vagus nerve) [18], tryptophan metabolism [63], gut hormonal response [64], and bacterial metabolites [32]. The gut microbiota can influence the central nervous system through the ability to synthesize or mimic a wide range of neuroactive molecules, such as acetylcholine, catecholamines, gamma-aminobutyric acid, histamine, melatonin, and serotonin (5-hydroksytryptamine) [27]. CNS functions can also be affected by short-chain fatty acids, which are products of carbohydrate fermentation and are able to enter the systemic circulation [65–67]. Moreover, bacteria of intestinal microbiota secret various neurotrophins and proteins, such as brain-derived neurotrophic factor (BDNF), synaptophysin and post-synaptic density protein (PSD-95) [68, 69]. Karakuła-Juchnowicz et al. [70] claim that there are some other factors that can influence the gut-brain axis, such as:

1) intestinal microbiota;
2) leaky gut syndrome;
3) oversensitivity to food antigens, including gluten and cow milk casein.

Hormonal, neuronal and bacterial changes in the intestines are transmitted straight to the brain via the vagus nerve, which forms a direct connection between gastrointestinal tract and the brain [71–73]. Pathways involved in bidirectional communication between the gut and the brain are presented in Table 2 [17]. While the enteric nervous system can function independently from the central nervous system, the intestinal microbiota and enteric nervous system constantly influence central nervous systems [74–76].Neurons of the enteric nervous system have their endings in the gut epithelial lining and are able to respond directly to luminal contents or indirectly to neurochemicals produced by the intestinal microbiota or endocrine cells [76, 77] and what is more, they can also communicate via the vagus nerve [78].

Table 2. **Bidirectional communication between the gut microbiota and the brain (own elaboration)**

Pathway	Effect
AFFERENT ARM	
Modification in composition of intestinal microbiota due to intake of antibiotics or probiotics	Changes in the levels of circulating pro/anti-inflammatory cytokines, which affect brain functioning
Generation of neurotransmitters or neuromodulators	Epithelial cells release molecules that stimulate axons
Influence on tryptophan metabolism	Changes in behavior
EFFERENT ARM	
The hypothalamic–pituitary–adrenal axis activation	Changes in gut permeability, motility, secretion, gut microbiota composition due to regulation of immune cells
Activation of regulatory areas of satiety in central nervous system	Impact on nutrient availability to intestinal microbiota and thus on gut microbiota composition

As described above, various afferent and efferent pathways are involved in the functioning of the gut-brain axis. Antibiotics, environmental and infectious agents, intestinal neurotransmitters/neuromodulators, sensory vagal fibers, cytokines, and essential metabolites – all convey information about the intestinal state to the central nervous system. As the connection is bidirectional, the hypothalamic-pituitary-adrenal axis, the central nervous system regulatory areas of satiety and neuropeptides released from the sensory nerve fibers can affect intestinal microbiota composition directly or using nutrient availability. Interactions mentioned above may influence the pathogenesis of a number of disorders, in which inflammation is involved – mood disorders, ADHD, autism [17]. Chrobak et al. [79] claim that low-grade inflammation may play an important role in pathophysiology of depression and disturbances of homeostasis of intestinal microbiota may represent one of the causes of such an inflammation.

Stress is one of the most important factors that influence the intestinal microbiota and are an inherent element of current everyday life. The composition of intestinal

microbiota is influenced both by emotional and physiological stress [80]. Dinan and Cryan [81] reported that healthy students during an extremely stressful time had fewer *Lactobacilli* present in their stool in comparison to less stressful periods.

Speculations that psychiatric patients may benefit from therapeutic modulation of the gut microbiota are growing in number, but this subject still needs further examination [82]. The latest research sought to reflect the functioning of the gut-brain axis with the use of brain imaging techniques and the measurement of the subconscious and conscious brain response to emotional stimuli, which may be abnormal in people with anxiety disorders or disorders of serotoninergic neurotransmission [83].

The intestinal microbiota and neuropsychiatric diseases

As far as the neuropsychological diseases are concerned, it is worth mentioning that the intestinal microbiota can convert undigested carbohydrates into short-chain fatty acids (SCFA), like acetate, propionate or butyrate. These SCFAs are able to bind and activate G-protein-coupled receptors (GPR 41 and GPR 43) on gut epithelial cells, leading to the secretion of peptide YY (PYY), which suppresses gut motility and retards intestinal transit [84]. SCFA also have an ability to activate GPR 120 receptor, which improves glucose metabolism, leads to release of GLP-1 and plays role in maintaining immunological homeostasis (reduction of inflammation) [85]. Moreover, propionate may induce autistic-like phenotypes in rats [86].

Autism spectrum disorder (ASD) is one of neuropsychological disorders in which the intestinal microbiota plays a key role. Recent studies have shown that microbiota composition in ASD patients differed from that of the healthy controls [87]. A significantly elevated level of *Clostridium* was found in patients with ASD [88–90]. Further evidence of the role of microbiota in autism spectrum disorders is confirmed by an observation that the application of antibiotics and probiotics led to an improvement in behavior and communication skills in ASD patients [91].

Depression is nowadays one of the most commonly diagnosed psychiatric disorder and has also been recently linked with changes in the gut microbiota. Underrepresentation of *Bacteroidetes* accompanied by overrepresentation of *Alistipes* – a genus in the phylum of *Bacteroidetes*, was found in patients with depression [92]. *Alistipes* has also been overrepresented in other diseases, such as chronic fatigue syndrome [93].

Quality and quantity of intestinal microbiota also seem to affect mood disorders and feelings of anxiety. Anxiety and depression are highly co-morbid in irritable bowel syndrome (IBS) patients [94]. In the study of Rao et al. [95], supplementation with *L.casei Shirota* decreased anxiety in patients with chronic fatigue syndrome.

Intestinal microbiota seems to play an important role in pathogenesis of many disorders, for example those mentioned in Table 1, but its mechanisms require further examination to allow us to use the knowledge on this subject in the treatment of these disorders.

New possible ways of treatment of mental disorders including modification of intestinal microbiota composition

Studies showed that the so-called "unhealthy" diet, i.e., the diet rich in sugar, fat-rich diet, ,and "western" diet – low in indigestable polysaccharides may be correlated with presence of depression and also can be its risk factor. Moreover, it has been observed that dietary improvements, such as introduction of Mediterranean-style diet, which is a gold standard healthy eating model, intake of fermented food, dietary fibre, plant-based diet and consumption of prebiotics – oligosaccharides, fructans can reduce risk of developing depression [91, 92]. New technologies provide better understanding of how important the diet is in the context of gut microbiota composition and possible advantages of the use of pre – and probiotics, and fermented food, especially when mental health is concerned. The association between diet in humans and prevalence of depressive disorders has been recently established [96–98]. Lai et al. [98] published a meta-analysis (based on 13 observational studies) on the basis of which it can be concluded that a healthy diet is associated with a reduced odds for depression (RR 0.84). Similarly, meta-analysis of 22 studies investigating the influence of Mediterranean diet on the occurrence of neuropsychiatric disorders, demonstrated that this diet was associated with a reduced risk of depression (RR 0.68) [96]. Moreover, increased consumption of sugar and unhealthy fat-rich food is related to an increased risk of psychological disorders in children and adolescents [97]. Two recent trials indicated the efficacy of dietary improvement as a strategy to alleviate symptoms of depression or even to prevent this illness [99, 100]. Stahl et al. [100] conducted a randomized study with 122 participants, aged ≥ 50 years with score ≥ 11 in the CES-D (Center of Epidemiologic studies Depression Scale) and ≥ 24 in the MMSE (Mini-Mental State Examination). Study consisted of treatment phase, i.e., 6–8 sessions over a 6–12 week period and additional sessions 3, 9 and 15 months after finishing the treatment phase. The mean age of the participants was 65.6 years, 71% of them were women. 95 participants, i.e., 77.9% of participants completed the 2-year study. Participants experienced a 40–50% improvement in depressive symptoms, with the BDI score decreasing from 9.92 to 5.93 after 2 years of diet modification.

In 2013, Sánchez-Villegas et al. [99] published randomized study from which it can be concluded that Mediterranean diet enriched with 15g of walnuts, 7.5g of hazelnuts and 7.5g of almonds per day may decrease the risk of depression by 41% in patients suffering from diabetes type II, comparing to the control group.

What is particularly interesting, there is evidence that microbiota can even affect for the selection of specific food products by the host [101]. Microbes may do this using two strategies – the first one is generating cravings for food that they desire or food that suppress their competitors, and the second one is to induce dysphoria until we eat food that enhance their fitness. Biota can do this using numerous mechanisms:

a) impact on reward and satiety pathways;
b) production of toxins that alter mood and may increase appetite;
c) impact on receptors, including taste receptors and as a consequence – effect on eating behavior, and altering cannabinoid and opioid receptors in gut;
d) taking control over the vagus nerve, the part of the brain-gut axis (blocking the vagus nerve should reduce food cravings and lead to weight loss) [101].

However, the phenomenon described above is not always beneficial for the host, as he/she can provide the food for pathological bacteria. What is more, an increased diversity of intestinal microbiota may limit bacteria's control over dietary choices of their host [101]. Whitaker et al. [102] claim that patients with depressive syndromes may crave for food rich in sugar and saturated fats. It was also found that depressive symptoms statistically insignificantly correlated with the consumption of sweetened beverages [101, 102], which can lead to negative changes in the microbiome, which in turn can cause exacerbation of depressive symptoms [91]. Dietary manipulation, including consumption of prebiotics and fermented foods, results in specific changes in the activity of gastrointestinal microbiota and this knowledge may be utilized in the treatment of depression and other disorders [103]. Diet is an easily accessible and effective tool for modifying composition of intestinal microbiota and may be more acceptable not only as a support but maybe in the future as an alternative to drug therapy (especially in patients with mild symptoms of depression). Although prebiotics and probiotics seem to be useful in psychiatry, holistic dietary changes may be necessary to provide long-term improvements in patients' general health [93].

Although the first probiotic treatment for depression was implemented in 1910 [104], the interest in microbiota and probiotic treatment has increased in recent years and now in the USA the annual market for non-prescription probiotics is estimated at one billion USD [105]. In 2016, Huang et al. [106] published a meta-analysis which showed that probiotics intake significantly improved depressive symptoms. Moreover, probiotics had an effect not only on the healthy population but also on patients with major depressive disorder. Probiotics had a positive effect on the participants aged under 60 years, whereas it had no effect on the people aged over 65. It is suggested that the microorganisms can form a new group of drugs named "psychomicrobiotics" [36]. In a double-blind, randomized clinical trial it was found, that healthy subjects who were given a mixture of probiotics, containing *Lactobacillus helveticus* and *Bifidobacterium longum* for 30 days demonstrated significant alleviation of symptoms of depression and anxiety reflected in score decrease in the HADs (Hospital Anxiety and Depression scale) and the HSCL-90 (Hopkins Symptoms Checklist) in comparison to the placebo control group [107]. It is also suggested that administration of the probiotic bacteria may be able to reduce inflammation, restore epithelial barrier function and potentially alleviate behavioral symptoms in children with autism [91]. Interestingly, in the study on rat offspring separated from their mother and placed in two different

groups – one group treated with *Bifidobacterium infantis* and the other with citalopram (30 mg/kg in drinking water) – Desbonnet et al. [108] revealed that probiotic therapy led to a reversal of behavioral problems and normalization of the immune response and norepinephrine levels in the brain. Moreover, no differences in corticosterone and cytokine concentrations were observed between the groups treated with escitalopram and *Bifidobacterium infantis*.

Another method to modulate the composition of intestinal microbiota is fecal microbiota transplant (FMT). To be precise, fecal microbiota transplant can be administered either as a suspension in saline, a highly refined liquid product, which can be frozen, or administered in a form of lyophilized powder in capsules or as an encapsulated spore preparation [109]. Each form is equally effective according to Jiang et al. [110]. So far, the FMT has been used as a treatment in *Clostridium difficile* infections, irritable bowel syndrome and inflammatory bowel diseases [111], but it can also be applied in the treatment of non-gastrointestinal diseases, especially neurobehavioral disorders which are associated with gut-brain axis [2, 112], as well as neurodevelopmental and psychiatric disorders [112–114]..The efficacy of FMT should be further evaluated, especially in mental disorders therapy. This approach to treatment has numerous advantages, including availability of source material, low cost of such therapy and lack of significant adverse effects. Moreover, Jiang et al. [115] showed an increase in the acceptance of FMT as a method of treatment among patients.

To sum up, modulations altering gut microbiota can be helpful in the treatment of many common diseases, especially mental disorders. in the future, after further examination, interventions such as changing diet, supplementation with prebiotics and probiotics, or even FMT may constitute a new possible way of improving patients' condition and health.

Conclusions

The knowledge on the influence of intestinal microbiota on human health is still increasing. Gut microbiota plays an important role both in health and in pathological states. Disruption of its quality and quantity may lead to states of dysfunction and occurrence or exacerbation of many common disorders. Connection between intestinal microbiota and human cognitive function maybe of great relevance in mental health disorders in the general population. Since the mechanisms of many psychiatric disorders still remain only a hypothesis and an effective treatment is yet to be found, any new possible way of treatment of these stigmatizing diseases should be taken into consideration. Interventions involving a modification of intestinal microbiota may set a new opportunity in the treatment and prevention of many diseases, particularly the psychiatric ones. However, this topic still needs further evaluation and more research should be conducted to provide understanding of the role of intestinal microbiota in the fundamental physiological and pathophysiological processes.

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