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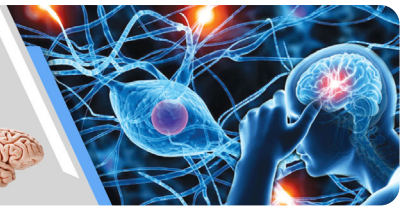

The Psychic Gut: Do Gut Flora Constitute the Next Psychiatric Treatment?

Margalit Izakson[1] and Gil Zalsman[1,2,3*]

Abstract

The microbiota consists of a vast bacterial population that resides mainly in the large intestine and lives in a symbiotic relationship with the host. The microbiota has significant physiological functions, including in the protection against pathogens, in maturation and shaping of the immune system, in metabolism and in the tendency towards obesity. The gut flora plays a major role in the bidirectional communication between the gastrointestinal tract and the central nervous system. The gut-brain axis is enabled by signals from the nervous system, hormones and the immune system. This review describes recent research that shows the influence of the microbiota on brain development, behaviour and mood. The possibility that perturbation of the gut bacteria may lead to psychiatric disorders will be discussed as well as the potential of new microbiota-based therapeutic interventions.

Keywords: Microbiota; Gut-brain axis; Psychiatric disorders; Development of the nervous system; Immune system

Establishment and Development of the Gut Microbiota

The microbiota consists of a collection of microorganisms, mostly bacteria, living in symbiosis in the human body and comprising in part the normal flora. The human digestive system and primarily the large intestine, contain the densest population of microorganisms in the body – over 100 trillion, namely 10-fold the total number of human cells. The microbiome - the collective genomes of the microbiota, contains 100 times more genes than the human genome. Thus, a human may be viewed as a mélange of species. The composition of the gut microbiota was discovered in the last few years due to both culture-based studies and culture-independent molecular methods based on sequencing bacterial ribosomal RNA genes (16S rRNA). It was found that the bacterial divisions populating the human gut are composed of two dominant ones: bacteroides and firmicutes and a third, less frequent one - proteobacteria. On the other hand, the microbiota is highly diverse at the species and strain level with over 500 species and 7000 strains [1]. The microbiota plays significant physiological roles in the development and regulation of the immune system, protection against infections [2], metabolism of food and medications and in the regulation of fat deposition and obesity [2,3]. In healthy people the microbiota population is relatively stable over the years and benefits the host. Bacterial composition and activity may be affected by nutrition, use of antibiotics, stressful events and by changes in digestion rate [4].

During birth new-borns are exposed to the maternal flora, which constitutes the basis for the development of the child's microbiota. Studies found that due to their passing through the birth canal, vaginal-delivery infants acquired

Affiliation:

[1]Geha Mental Health Center, Petah Tikva, Israel

[2]Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

[3]Molecular Imaging and Neuropathology Division, Psychiatry Department, Columbia University, New York, NY

***Corresponding author:**

Gil Zalsman, Director, Geha Mental Health Center, Petah Tikva, 4910002, Israel

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bacterial populations that were similar to their mothers' vaginal and gastrointestinal microbiota. Meanwhile, infants delivered by caesarean section were seeded with bacteria similar to that found on their mother's skin surface and in the hospital environment. Interestingly, infants born by caesarean section are at greater risk to develop, during their lifetime, allergies, asthma, type 1 diabetes, obesity and digestive disorders. This may be due to the pivotal role played by the microbiota in the shaping and maturation of the immune system [5].

It was also found that gestational age at birth influences the microbiota composition. Thus, prematurely born infants lack two principal bacteria populations that are present in full term infants [6]. Another major player in the continued transfer of the maternal flora to the infant is lactation, which is associated with lower rates of infections and better cognitive development [7].

The gut flora changes gradually during childhood so that the number of aerobic bacteria decreases while that of anaerobic ones increases [8]. During adolescence the microbiota population still undergoes remodelling, whereas in adulthood it stabilizes and becomes more diverse.

Further research is needed to elucidate the relationship between hormonal changes in puberty and the microbiota as well as the impact of microbial imbalance (dysbiosis) during this crucial period, in which many psychiatric disorders emerge. Clearly, both genetics and the environment influence the composition of the flora, as do infections, antibiotic use, diet and stress.

The Microbiota- Gut-Brain Axis

Increasing evidence suggests that the microbiota has a pivotal role in the bi-directional communication between the gastrointestinal tract and the central nervous system. This bi-directional communication involves neural and hormonal signals as well as signals from the immune system [9]. The relationship between these two systems affects the response to stress, pain perception and impacts on disturbances related to the gut-brain axis. Emotional factors such as depression and stress influence the progression of Inflammatory Bowel Disorder (IBD). Moreover, psychiatric disorders such as depression and anxiety are often comorbid with both IBD and functional disorders of the digestive system (e.g. irritable bowel syndrome (IBS)). IBD and IBS have been found to be themselves associated with dysbiosis in the gastrointestinal tract [10].

The brain can affect the function of the digestive system by altering the gastrointestinal motility, production and secretion of mucin and secretion of cytokines by the immune system [9]. Different emotional states such as stress can alter the intestinal permeability, motility and secretions, by releasing stress hormones or activating the sympathetic system, thus changing significantly the microbiota environment, composition and functionality. For example, it has been shown that inducing stress in mice changes the composition of their gut microbiota by reducing the bacteroid population and increasing clostridium species. These changes were accompanied by an increase in pro-inflammatory cytokines. Stress hormones can also impact gene expression and signalling-pathways among the microbiota, thereby altering their function [10,11].

The gut flora may influence the brain and modulate behaviour via several mechanisms. Metabolites produced by the microbiota may reach the brain through the vasculature of the area postrema and influence activity and behaviour. Bacterial fermentation products like lactic and propionic acids were found to be associated with anxiety and memory impairment in rats [12] and anxiety in IBS patients [13]. Additionally, carbohydrate malabsorption, which increases the amount of products available for bacterial fermentation, was found to be associated with early signs of depression in women [14].

The gut microbiota also produces neurotransmitters and regulates the availability of their precursors, thereby potentially affecting brain and behaviour. Studies have shown that the gut microbiota regulates the levels of circulating tryptophan and its metabolites. When germ-free mice are colonized, there is an increase in tryptophan metabolism that is associated with elevated levels of serotonin. It was also found that certain strains of gut bacteria are able to produce the inhibitory transmitter GABA and monoamines such as noradrenaline, serotonin and dopamine [15].

The microbiota may communicate with the brain through the immune system. Studies have shown that the gut bacteria are able to change the profile of secreted cytokines from pro-inflammatory to anti-inflammatory. Pro-inflammatory cytokines like Interleukin-4 (IL-4) and Interferon γ were found to be involved in depression [16]. The adaptive immune system itself and especially the T-cells were found to play a significant role in adult neurogenesis, spatial learning and memory and in coping with stress [17,18]. Other studies have suggested the vagus nerve as a possible communication pathway between gut bacteria and the brain [11].

Gut Microbiota Affects Brain Development and Behaviour

Formation and development of the gut microbiota occur early in life, parallel to that of the nervous system, suggesting shared and interacting critical developmental windows. Accumulating data imply that perturbations of the gut microbiota during significant, dynamic brain development periods, such as the pre-natal period or adolescence, may damage the neurodevelopmental process and lead to psychiatric disorders later in life [19].

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Traditionally, the intrauterine environment and the foetus are considered sterile until birth. Preliminary studies of recent years however, have shown presence of maternal flora bacteria in the intrauterine environment. It is suggested that these bacteria travel from the maternal gut into the systemic blood system and on through the placenta and the umbilical cord into the amniotic fluid. Thus, potentially establishing in-utero, the foetus' first microbiota population [20]. Studies in germ-free mice demonstrated the ability of the microbiota to influence brain development early in life, by altering the Hypothalamic-Pituitary-Adrenal (HPA) axis. These mice showed exaggerated response to stress, which normalized after monocolonization with Bifidobacterium Infantis. Interestingly, it was found that the window of opportunity for repairing the stress response is confined to the first few weeks of life, emphasizing the importance of early exposure to microbiota for the HPA axis to function normally [21].

Other studies have shown that germ-free mice display reduction in anxiety behaviour in the elevated plus maze and increase in motor activity and in risky behaviour. This behaviour was normalized after colonization in early stages of life. These behavioural changes were accompanied by an increase in hippocampal expression of Brain-Derived Neurotrophic Factor (BDNF), decrease in the levels of the serotonin receptor 5-hydorxytryptamine (5-HT1A) and changes in protein levels related to synaptic plasticity like synaptophysin and postsynaptic density protein 95 (PSD 95). Germ free mice also show dysfunction of working memory that may indicate abnormal development of the hippocampus [22].

Temporary alterations in microbiota can influence behaviour as well. For example, dietary manipulation in mice (beef-enriched diet) modified the composition of the gut flora and was associated with improved memory and learning abilities and a decrease in anxiety [23].

Further support for the notion that gut flora mediates behavioural changes comes from a study, which showed that transplantation of microbiota from one strain of mice to another induces in them typical behavioural characteristics of the donor strain. The behavioural changes were accompanied by alterations in BDNF levels in the hippocampus [24]. Collectively, these studies suggest that the gut microbiota influences behaviour, at least in part, via neurochemical changes and modulation of neural circuits. Accordingly, perturbations in the bacterial population may lead to CNS disorders and adverse mental health outcomes.

Microbiota and psychiatric disorders

Emerging data suggest possible interactions between the gut microbiota and Autism Spectrum Disorders (ASD). ASD is a complex neurodevelopmental disorder resulting from the combination of genetic and environmental factors however the aetiology is still unknown. In addition to social and behavioural impairments individuals with ASD frequently suffer from gastrointestinal disturbances, implying a putative role of the gut microbiota in the pathophysiology. Several studies suggested that gut dysbiosis may be involved in some cases of late/regressive ASD that commences past 18 months of age and is often accompanied by digestive disorders such as abdominal bloating or pain and changes in bowel habits. Interestingly, it was found that in some regressive cases, oral administration of vancomycin improved temporarily the ASD symptoms. Accumulating data suggest that the profiles of the gut flora in individuals with ASD are different from those of the general population. Amongst others, it was found that people with ASD had less amounts of bacteroidetes leading to significant increase in the firmicutes/bacteroidetes ratio. It was also found that the intestinal flora of children with both, ASD and gastrointestinal disturbances, contained high levels of Sutterella species, which were absent in control children.

Studies in germ-free mice found social deficits and increased stereotypical behaviour, similar to that appearing in ASD patients. In a mouse model for ASD it was shown that treatment with the bacterium Bacteroides Fragilis, that is part of the normal gut flora, at the onset of puberty, improved some of the deficits that are characteristic for ASD [25].

The mechanisms responsible for the association between the microbiota and ASD are still unknown. It could be that already in uterus metabolites secreted by the microbiota reach the CNS and have adverse effects on the neural tissue to which they gain access via the maternal circulation and the placenta. In a rat model it was shown that intraventricular administration of propionic acid that is produced, amongst others, by the gut-bacteria, caused ASD like behaviour, which was accompanied by neuro-inflammatory processes [26].

So far, studies on the relationship between gut microbiota and depression have been performed mostly on rodents. A study that used the rat maternal separation model - a common paradigm to investigate mood disorders, demonstrated that administration of probiotics (Bifidobacterium Infantis) had the same effect as the antidepressant citalopram. Both treatments reversed the behavioural deficits and normalized the inflammatory response and the levels of noradrenaline in the brain [27]. Only few clinical studies investigated the connection between depression and microbiota. Preliminary studies demonstrated differences in the composition of the microbiota population between individuals with depression and the general population. Additionally, it was shown that by transplanting faeces that contain microbiota from people with depression to germ-free mice or rats lacking gut-flora as a result of antibiotic treatment, it is possible to induce certain behaviours and depressive symptoms [28]. Clinical studies investigating the influence of probiotics administration on depression and anxiety in healthy subjects,

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found that administration of probiotics vs. placebo decreased significantly anxiety levels, feelings of distress and negative mood that were reported in questionnaires prior to and following that treatment [29].

Depression is associated with a chronic low grade inflammation. A putative influence of the gut microbiota in major depression has been suggested as part of the leaky gut theory, which describes a gut that functions improperly as a barrier and is permeable to pathogens and toxins to enter the blood system, thus causing an inflammatory response via the immune system [30]. Studies in animals have shown that probiotics administration may prevent "leaky gut" [31].

Future directions

Research on the relationship between microbiota and the brain is still in its infancy. For now there are more open questions than there are answers. Pre-clinical and clinical studies are needed in order to elucidate the mechanisms by which the gut microbiota communicate with the brain. It is also necessary to continue mapping the composition of the bacteria population during various stages of life and investigate gender differences as well as bacterial population profiles in various neurological and psychiatric disorders.

The hypothesis that the composition of the flora may have far-reaching influences on brain development carries the hope for early interventions and novel treatments such as administering probiotics to pregnant women and to infants delivered by caesarean section or prematurely, promoting breast-feeding and administering probiotics to psychiatric patients.

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Conflict of Interest

None of the authors report any conflict of interest with regard to this study.

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