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# Influence of Gut Microbiota on Behavior and Its Disturbances

*Valentina Ignatova*

## Abstract

Hippocrates statement that “All disease begins in the gut” continues to be up to date more than 2000 years later. Growing number of scientific reports focus on the important role of intestinal microorganisms for modulation of many systems and human behavior. As a key component of the gut brain, gut microbiota influences the development and maturation of the hypothalamic-pituitary-adrenal axis, affects the development and function of the immune system, regulates the blood-brain barrier, modulates the synthesis and recognition of neurotransmitters, regulates neurogenesis, formation of myelination and supports the development and function of the brain. Disruption of gut-brain axis function is associated with alterations in the stress response and might contribute to neuropsychiatric diseases as depression, autistic spectrum disorders, rapid eye movement sleep behavior disorder, Parkinson disease, Alzheimer disease and other mental conditions. Studies in animal models are crucial for guiding research on brain-gut-microbiome axis in humans, as the impact of microbiota on specific brain regions and aspects of animal behavior will help in the selection of tasks for cognitive assessment. Exploring the interaction of gut microbes and human brain will not only allow us to better understand the pathogenesis of neuropsychiatric disorders, but will also provide us new opportunities for the design of novel immuno- or microbe-based therapies.

**Keywords:** gut microbiota, brain, gut-brain axis, behavior disturbances, modulation, human behavior, animal models

## 1. Introduction

Hippocrates statement that “All disease begins in the gut” continues to be up to date more than 2000 years later. The fields of microbiology, gastroenterology and neuroscience have evolved gradually over time and remarkable progress in modern medicine has been achieved not only in their individual trajectories, but also in their active interaction. It has recently become evident that gut bacterial flora can greatly influence all aspects of physiology, including gut-brain communication, brain function and even behavior [1].

The population of microorganisms, localized in the human gut and consisting of bacteria, viruses, protozoa, fungi etc., definitely exceeds the number of cells that make up the human body. The collection of these microorganisms, their genomes and the factors that they produce are all part of the gut microbiome [2, 3]. The role of microorganisms that make up the intestinal flora can be identified as pathogenic, neutral, or useful for the host. The beneficial bacteria known as probiotic bacteria predominate in the intestine of healthy subjects. The word probiotic has

Greek origin and its meaning states “for life”. In fact, probiotics are referred to live microbes which are important for maintaining the intestinal microbial balance and have the capacity to keep and improve the health of their human host” [4–6].

The intestinal microbiota and its metabolites influence modulation of gastrointestinal (GI) functions through their ability to affect gut permeability, mucosal immune function, intestinal motility and sensitivity, and also activity of the enteric nervous system (ENS) [6, 7]. Multiple mechanisms, including endocrine and neurocrine pathways, are suggested to be involved in gut microbiota-brain signaling. On the other hand, the brain can in turn alter microbial composition and behavior via the autonomic nervous system (ANS) [8].

Evidences from studies in rodents raised in a germ-free (GF) setting pointed that the gut microbiota influences the development of emotional behavior, stress- and pain-modulation systems and brain neurotransmitter systems. Furthermore, perturbations of microbiota occurring as a result of probiotics and antibiotics application exert lead to effects on some of these modalities in adult animals [8–11].

The absence of micro-organisms in the gastrointestinal tract (GIT) of mice shows a reduction in the number of Peyer’s patches and IgA producing B-cells in the lamina propria versus healthy controls, whereas the introduction of microbes reverses these effects [12, 13]. It is curious that, GF mice also provide evidence of an overactive hypothalamic-pituitary-adrenal (HPA) axis and reduced monoaminergic activity, suggesting that microbial colonization can have lasting effects on central systems, which are involved in the psychopathology of depression [14].

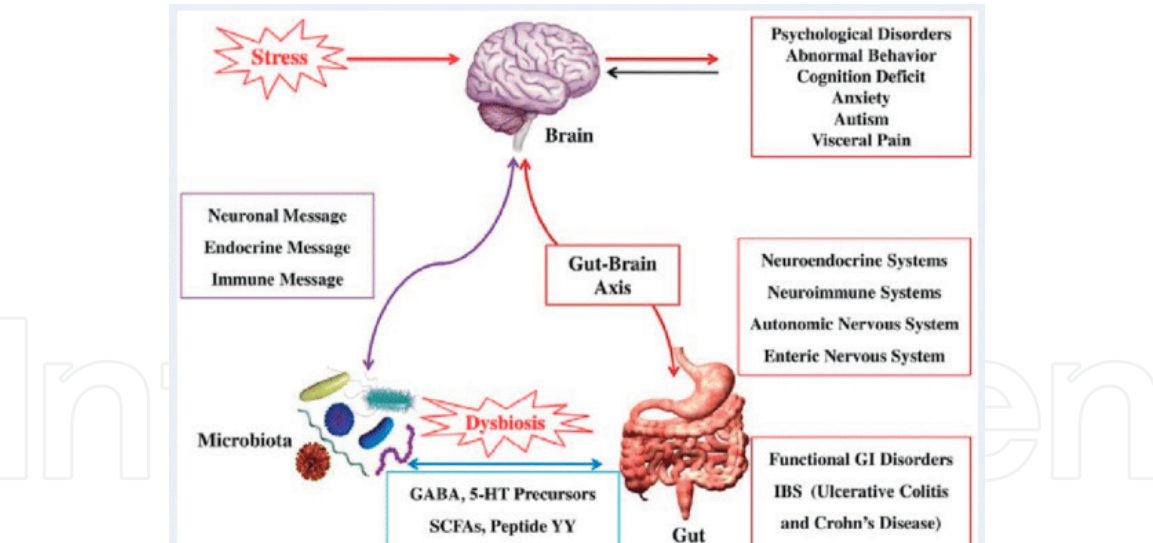
Some of the most common species/probiotics are bifidobacteria. Shortly after birth, up to 90% of the bacteria found in children’s GIT are bifidobacteria, and in adults they still account for approximately 3–5% of the microflora [15]. Moreover, in inflammatory diseases such as irritable bowel syndrome (IBS), treatment with bifidobacteria normalizes the existing disequilibrium between pro-inflammatory and anti-inflammatory cytokines in this disease [16, 17]. Based on the established important role of the balance between anti- and pro-inflammatory cytokines in the pathophysiology of depression [18, 19], it can be hypothesized that probiotics may have potential antidepressant properties. Of course, the potential benefits of probiotics as adjuvant therapy in depression are currently being discussed [20]. A recent study of Benton et al. has demonstrated a beneficial effect of long-term probiotic treatment on the mood of healthy subjects [5, 21].

It is supposed, that the violation of the two-way functional connection between brain and gut microbiota take a part in the pathogenesis of certain diseases of “gut-brain-axis” such as IBS and impairments of GI-functionality [1, 22] but it could be also involved in the pathogenesis of a lot of significant neuropsychiatric diseases: autism spectrum disorders (ASDs) [1, 23], Parkinson’s disease [24], mood disorders [25]; and chronic pain conditions [1, 5, 26].

Unfortunately, the information how these findings could be transferred to healthy humans or to disease states involving the brain or the gut-brain axis is still insufficient. Further research with focus on this topic for translation to human physiology and to diseases such as irritable bowel syndrome, autism, anxiety, depression, and Parkinson’s disease should be performed [8].

The interaction between gut microbiota and brain at the levels of gut-brain axis and their influence on manifestation of gastrointestinal, mental and neuropsychiatric diseases is presented at **Figure 1**.

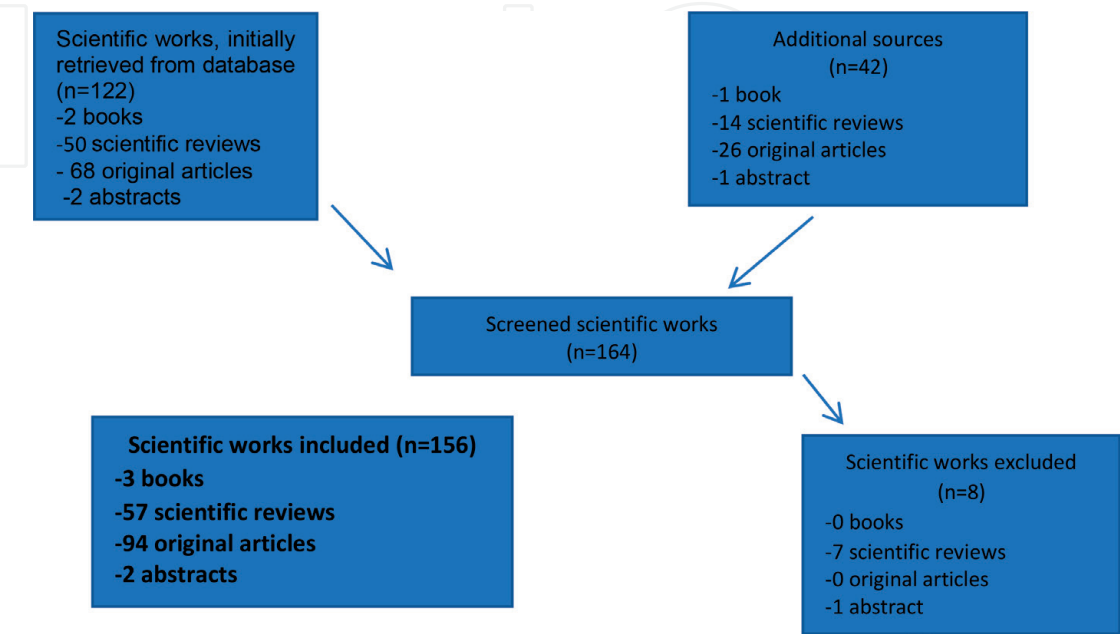
The aim of the review is to examine the dependence between the functioning of microbiota-gut-brain axis and human behavior and how it can contribute to a better understanding of human psychology and choosing an appropriate therapeutic approach in cases of behavior disturbances.



**Figure 1.**  
*Bidirectional interactions between gut microbiota and brain. Relationship with medical conditions [27].*

## 2. Method of searching

An advanced search was performed in electronic database (PubMed, MEDLINE), based on the combinations of the following key words and phrases as entry screening criteria: “gut microbiota”, “brain”, “behavior disturbances”, “modulation”, “microbiota-gut-brain axis”, “influence of gut microbiota on human behavior”, “abruption of microbiota-gut-brain axis”, “animal models of interrupted microbiota-gut-brain axis”. The time period of the search was unlimited. The relevant information was selected from systematic reviews, meta-analysis, books chapters, original articles, conference abstracts and theses, published in English. The exclusion criteria targeted case reports which were not entered in the analysis. The reference of the related scientific sources from the selected articles was additionally checked and the relevant of them were also included in the recent work. A relationship between functioning of intestinal microbiota and human behavior was searched. Based on the above listed criteria, initially were retrieved 3 books,



**Figure 2.**  
*Method of searching.*

60 scientific reviews, 98 original articles, 3 abstracts. The final number of selected and really used scientific works was as follows: 3 book chapter, 57 scientific reviews, 94 research studies, 2 paper abstracts on the current topic “Influence of gut microbiota on behavior and its disturbances”—**Figure 2**. The chronology of knowledge regarding microbiota-gut-brain axis and its influence on human behavior was also tracked. The similarities of points of view and results, as well as the contradictions in published literature were analyzed. The possibilities for psychological and drug interventions in patients with behavior disturbances based on the summarized conclusions were also highlighted.

### 3. Role of gut-brain axis for mental health

The essential interaction between the gut and the brain through the gut-brain axis is well established. The environment and related factors render influence on central nervous system (CNS), as well as on HPA axis. Furthermore, the CNS interacting with the ENS, the intestinal muscular and mucosal layers via vegetative afferent and efferent tracts, modulates gut functions as permeability, mucus secretion, motility, as well as host immunity [13, 28, 29]. Thus, CNS inputs can affect the gut functions, while gut inputs could modify specific CNS processes [1, 30]. Interruption of these bidirectional interactions may provoke neuroinflammation processes and could be involved in the pathogenic ways responsible for development of CNS disorders [13].

#### 3.1 Anatomy of the gut-brain axis

The functioning of the colon is modulated by both internal (intrinsic) and external (extrinsic) neural pathways [31].

##### 3.1.1 Intrinsic innervation

The ENS is integrative system of neurons with structural complexity and functional heterogeneity, similar to these of brain and spinal cord. Its main role is to control motility, secretion, mucosal transport and blood flow of the GIT [32]. The ENS realizes these functions via motor neurons, localized in ganglia, composing a final common pathway to the effector cells of the GIT. Although these specialized motor neurons receive some impulses from CNS through parasympathetic and sympathetic pathways, their function is predominantly coordinated by sensory neurons and interneurons localized within the ENS [30].

##### 3.1.2 Extrinsic innervation

###### 3.1.2.1 Splanchnic “sympathetic” nerves

Their noradrenergic fibers within the wall of the GI tract arise from cell bodies embedded in the prevertebral sympathetic ganglia. The major “sympathetic” projections to the large intestine originate from the inferior mesenteric ganglia and the remaining noradrenergic fibers to the rectum are provided by the pelvic ganglia.

###### 3.1.2.2 Vagal (parasympathetic) innervation

The vagal nerve transfers information between the internal organs and the brainstem. It contains both afferent and efferent nerve fibers and innervates the entire



gut with exception of the distal third of the colon. Vagal afferents terminate in the nucleus of the solitary tract (NTS) whose impulses go up through the parabrachial nucleus (PBN) to the thalamus, limbic system and insula [33, 34]. Spinal fibers pass up via the spinothalamic tract and the dorsal spine columns. Respectively, the spinothalamic pathway goes ascendingly to the thalamus, and the dorsal columns give projections to the gracile nucleus and cuneate nucleus in the upper medulla. Efferent impulses from the last rostral medullar structures reach the thalamus through the medial lemniscus. In turn, thalamic projections ascend to the primary somatosensory cortex and insula [30]. Vagus motor nuclei are represented by nucleus ambiguus (NA) and dorsal motor nucleus (DMN). The DMN is a source of efferents to the smooth muscles of the gut that form synapses with the neurons of the MP [7, 33].

### **3.2 Gut microbiota influences and human brain function**

#### *3.2.1 ANS modulation of the gut microbial environment*

Impaired intestinal transit caused by compromised migratory motor complexes (under parasympathetic modulation) is associated with an increased microbial colonization in the small intestine [5, 35–37]. The frequency of regular migrating motor complex is influenced by the number of feeds, quality of sleep and stress. Acute stress is associated with increased parasympathetic output to the small and large intestine and decreased vagal output to the stomach [38]. ANS affects the mechanisms of immune activation at the level of intestinal epithelium. This process could be influenced through modulation of the intestinal immune cells such as macrophages and mast cells against gut luminal microbes through antimicrobial peptides or indirectly via changing the access of gut microbiota to the intestinal immune cells [1, 39]. This process could be influenced through modulation of the intestinal immune cells such as macrophages and mast cells against gut luminal microbes through antimicrobial peptides or indirectly via changing the access of gut microbiota to the intestinal immune cells.

Preclinical studies proved that increased permeability of intestinal epithelium after exposure to different stressors is result of easier translocation of gut microbiota followed by driving of immune response [1, 40, 41].

#### *3.2.2 Effects of host's signal molecules on the function of the intestinal microbiota*

Neuronal and neuroendocrine signaling molecules as catecholamines, serotonin, cytokines, GABA, dinorphine, etc. dispersed into the gut lumen through neurons, immune and enterochromaffin cells can also play a role in the modification of intestinal environment [1, 8, 42], probably regulated by the CNS [43]. Many stress factors result to increasing of both plasma and luminal gut levels of catecholamines as norepinephrine [8, 44]. In vitro experiments indicated that some pathogen microbes could change their proliferative ability after exposition to exogenous catecholamines. Norepinephrine may accelerate the proliferation of several strains of intestinal pathogenic microorganisms and could increase the virulence of *Campylobacter jejuni* [1, 45, 46].

#### *3.2.3 Microbe-to-host signaling by microbial signaling molecules*

Metabolites produced by intestinal microbiota, including short chain fatty acids (SCFAs), bile acid metabolites and neuroactive agents such as GABA, tryptophan precursors and metabolites, serotonin and catecholamines, including free metabolites and cytokines released during the immune response to microbes may deliver

the signal to the host via local cell receptors in the intestine [37, 47]. These factors can also give signals via neurokinins through afferent vagal and spinal pathways and endocrine mechanisms to target non-GI tracts, including vagal afferents in the portal vein and receptors in the brain. A significant part of the metabolites identified in the circulation are with intestinal microbial origin [48, 49]. The enteroendocrine cells, as well as the neurons forming the submucosal and myenteric ganglia, express different types of SCFA receptors [50]. A diet that includes *Bifidobacterium breve* leads to elevated levels of fatty acids in the brain, but unfortunately there is not a clear explanation for that mechanism [1].

Actual studies confirm that multiple nuclear receptors (NRs) are expressed in the GI tract and several microbe-produced metabolites act as ligands of NRs. Intestinal bacteria secrete metabolites including indole derivatives, hormones and secondary BAs, which play role of natural ligands for the host's NRs [51]. In this way the microbial metabolites can realize biological effects in the human body via regulation of the host's gene expression. These dynamic interactions permit overall control on the health or disease development in the host through direct effect of the microbiota on the human physiology [11]. Via signaling to the brain, the microbiota regulates metabolism, CNS development, inflammation as well as mood and behavior. It is essential that the human host has the ability to voluntarily influence and meliorate its own microbiota through nutritional or probiotic interventions [52].

Latest research found that, in the presence of the microbiota, the intestinal epithelial lining generates physiological levels of oxidative stress. On the other hand, these interfere both with the composition and functionality of the microbiota (e.g., anaerobes thrive in the presence of electron acceptors) and directly with the gut permeability. This lead to increased probability of xenobiotic molecules to reach the systemic circulation as well as the CNS [53].

Another well-known interaction between the microbiota and CNS involves astrocytes. Astrocytes represent a functionally diverse group of glial cells, which are responsible for ion homeostasis, neurotransmitter balance, storage of glycogen, the integrity of the blood brain barrier (BBB), realizing of the neuronal signaling, which play a main role in the neuroinflammation process [54]. The inflammation could be suppressed by modulation of type I interferon signaling in astrocytes, initiated by microbial metabolite products, which activate the aryl hydrocarbon receptors (AhRs). The indoles, released from gut microbiota, act as AhR agonists [55]. The dietary tryptophan in intestinal cavity, which is undigested, is transformed into indole in the presence of the microbial enzyme tryptophanase. Then the indoles could be modified through microbial or viler enzymes to indole derivate with various affinity [10, 56].

#### **4. Dysregulation of the gut-brain axis. Evidences from experiments on animals**

Alterations in the microbial contain of the GIT are considered to contribute to inflammatory and functional bowel disorders and psychiatric comorbidities. The results of recent studies using various strains of mice and rats, various strains of probiotics and various experimental paradigms reported a number of microbial bowel modulation effects in emotional behavior [57–59], learning and memory [60], social interactions [61] and nutritional behavior [62].

##### **4.1 Experiments on mood changes in disturbed gut-microbiota in rats**

The first experiments in young GF mice which confirmed the influences of gut microbiota on postnatal development of the hypothalamic-pituitary response

to stress were performed by Sudo et al. in 2004. It is interesting, that the GF mice expressed reduced anxiety-like behavior in the elevated plus maze (EPM), a reliable behavioral test that examines approach and avoidance behavior in mice, compared to specific pathogen free (SPF) mice [63].

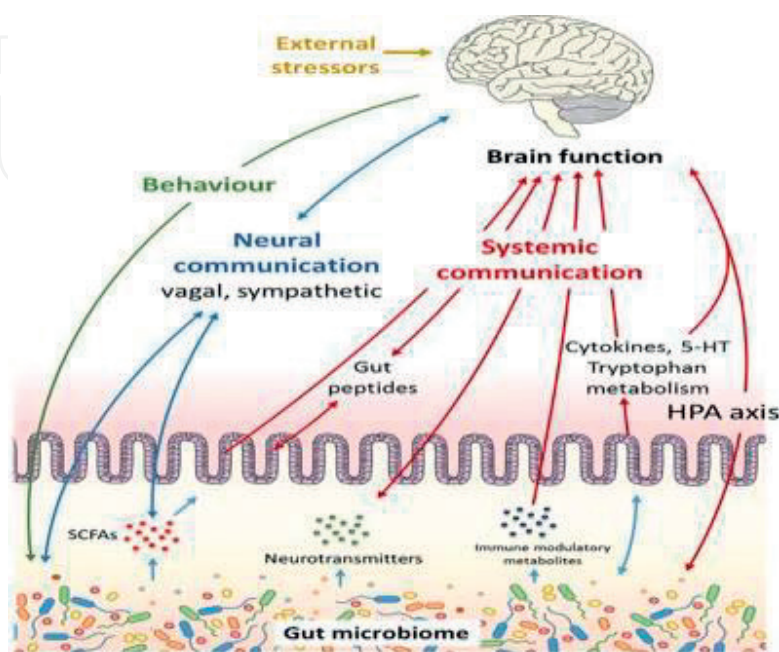
Desbonnet et al. evaluated the potential antidepressant properties of probiotics through testing of rats chronically treated with *Bifidobacteria infantis* in the forced swim test [5]. Probiotic administration in naive rats had no effect on swimming behaviors. However mitogen stimulation in probiotic treated rats lead to substantial reduction of IFN- $\gamma$ , TNF- $\alpha$  and IL-6 cytokines compared to controls ( $p < 0.05$ ). In addition, the plasma concentrations of tryptophan ( $p < 0.005$ ) and kynurenic acid ( $p < 0.05$ ) were significantly elevated in the rats, treated with bifidobacteria [20]. Treatments with *Bifidobacteria* also lead to reduced 5-HIAA concentration in the frontal cortex and a decrease in DOPAC in the amygdaloid cortex [5].

Schroeder et al. provided evidences for production of benzodiazepine ligands in a rat model of encephalopathy or butyrate acting as a histone D-acetylase that was shown to have an antidepressant effect [64, 65].

The study of Arseneault-Breard et al. gave the first evidences for beneficial effect of probiotics *L. helveticus* R0052 and *B. longum* R0175 on post-myocardial infarct depression in rats. This positive probiotic influence was engaged in maintaining of the gut barrier integrity, which is possibly associated with the host' inflammatory state after MI [84].

The association of increased HPA axis responses and reduced anxiety-like behaviors observed in several of the studies performed in GF mice suggests that HPA axis and nonhypothalamic (anxiety-like behavior) components of central stress circuits may be affected on different ways according to the GF conditions, depending on species and mouse strain. These findings suggest that the increased HPA axis activity in GF animals may represent a response of the organism to the loss of microbiota-related energy sources [8].

Savignac et al. demonstrated that the two *Bifidobacterium* strains used in their study were able to improve the anxious phenotype of innately anxious BALB/c mice in a strain-specific manner and the effect was better than that from the administered antidepressant escitalopram. These findings support the statement that probiotics could be a reliable alternative for treatment of mood disorders [142].



**Figure 3.**  
 Impact of gut microbiota and external stress factors on behavior [66].



On **Figure 3** is presented influence of both gut microbiota and external stressors on behavior.

#### 4.2 Experiments on behavior changes in disturbed gut-microbiota in rats

The increased hippocampal brain-derived neurotrophic factor (BDNF) registered in the ATM-treated mice is corresponding with their gregarious behavior. A recent study found increased BDNF expression in the amygdala during fear learning [67, 68]. Over activation of the amygdala also has been implicated in depression and anxiety [67, 69]. Lower levels of BDNF in the amygdala of ATM treated mice were associated with increased exploratory behavior.

Bercik et al. found that SPF mice who received antimicrobial agents per os demonstrated enhanced exploratory behavior and hippocampal expression of BDNF. This finding was associated with temporary alteration of the representatives of their microbiota and was not accompanied by inflammatory status, alteration of gastrointestinal neurotransmitters levels, nor with vagal or sympathetic function. Intraperitoneal application of antimicrobial agents to SPF mice, similar to their oral administration in GF mice had no influence on behavior. Increased exploratory behavior and high hippocampal levels of BDNF were reported in GF BALB/c mice, colonized with microbiota from NIH Swiss mice. Suppression of exploratory behavior was demonstrated in GF NIH Swiss mice, colonized with BALB/c microbiota [2, 70].

The study of Bercik et al. did not provide proof for intestinal inflammation, as oppose to Verdú et al.' investigation [71], where administration of ATMs in a higher dose and for a longer period was made in NIH Swiss mice. In the Bercik's experiment embarrassment of the intestinal microbes did not change myeloperoxidase activity, histology or cytokine profile of the colon [8]. No differences in serotonin, dopamine, or noradrenaline content in the gut of ATM-al. treated mice were observed, suggesting that these neurotransmitters are not involved in mediating the behavioral changes observed in the model.

Li et al. and Bercik et al. reached similar results on memory and learning skills in adult mice [11], applying different nutritional supplements to animals at a very early age with the following disruption of the intestinal flora in very young age. Working and referred memory was better in the animals on rich in beef diet as opposed to the mice on standard meal [8].

Neufeld et al. supposed that the low anxiety-like phenotype was accompanied by long-term changes in plasticity-related genes in the hippocampus and amygdala. They found altered GF behavior, accompanied by a decrease in the N-methyl-D-aspartate receptor subunit NR2B mRNA expression in the central amygdala, increased BDNF expression and decreased serotonin receptor 1A (5HT1A) expression in the dentate granule layer of the hippocampus. It is the first work which demonstrated an altered behavioral phenotype related with lack of gut microbiota [59].

In their work Bravo et al. registered increased levels of GABAB1b mRNA in cingular and prelimbic areas in mice treated for a long time with *L. rhamnosus* (JB-1), while the concentration of these neurotransmitters was reduced in the hippocampus, amygdala and locus coeruleus in the same experimental animals. Furthermore, the GABAA $\alpha$ 2 level was reduced in the prefrontal cortex and amygdala, and increased in the hippocampus. The observed mice expressed reduced response to stress, associated with releasing of corticosterone. Similar neurochemical and behavioral effects were not expressed in mice, who has underwent vagotomy [12, 73].

In their study Park et al. demonstrated that depressed-like behavior in mice that underwent bilateral olfactory bulbectomy (OBx) was associated with altered

colonic motility and a shift in the microbiota profile. Their experiment also supposed that increased prokinetic neuropeptide, gut hormone and serotonin in the colonic wall are mediators of the altered motility [25]. Their finding was consistent with those of Rodes et al. who showed changed colonic transit and altered stability of the colonial microbial community [74].

Hsiao et al. demonstrated GI barrier defects and microbiota alterations in the maternal immune activation (MIA) mouse model who displayed ASD signs. MIA generation, who has received *Bacteroides fragilis* (human commensal microbe) per os, has evolved altered bacterial gut content which predisposes to impaired communication and manifestation of stereotypic, anxiety and sensorimotor behavior. The described experimental model showed change in profile of the serum metabolites and their levels. It is other evidence for the gut microbiota impact on human behavior through the gut microbiome-brain functional axis and it could help in searching of relevant probiotic treatment of behavior disturbances in neurodevelopment diseases in human [3, 75].

It was found that gut microbiota status reduce social interactions in GF mice and probiotics improve social interactions in a post-MI rat model. Desbonnet et al. examined whether the degree of information transfer during social interaction is disrupted in GF mice. In their experiment GF mice spent a decreased proportion of time engaged in social investigation and substantially greater proportion of time engaged in repetitive self-grooming behavior during social interaction. After GF bacterial colonization these behaviors were normalized, which is evidence for involvement of microbiota in modulation of such behaviors. However, the quality of information transfer during the interaction was not affected in GF mice, indicating that the ability to process information per se during social interaction was not affected in GF mice [76].

It is important to note that many of the psychologic deficits, registered in GF mice, are specific to males in which higher incidence of neurodevelopmental disorders was registered compared to females [59, 63, 77–79]. de Theije et al. demonstrated that gender-specific inflammatory conditions are present in the small intestines of VPA in utero-exposed mice and are accompanied by a disturbed serotonergic system both in the brain and in the intestinal tract [80]. Gut microbiota-associated behavioral changes were reported in different ASD mouse models using valproic acid administration or maternal infection; in the latter instance some behavioral disorders were favorably influenced by probiotic therapy with *Bacteroides fragilis* [8, 9].

Several studies proposed the influence of intestinal microorganisms on eating behavior [80], probably as a consequence of modified fatty acid receptors, gut receptors, responsible for taste, alteration of the intestinal transportation mechanisms or disturbed releasing of satiety hormones [9, 81, 82].

Crumeyrolle-Arias et al. found that lack of intestinal microbiota in sensitive to stress strain rats lead to neuroendocrine and behavior reactions of acute stress and significant changed degree of the dopaminergic turnover in the higher brain structures which modulate stress and anxiety—another support for the crucial impact of the gut microbiota on the higher brain activities [9, 15, 83, 84].

Recently it was reported that impaired permeability of the blood brain barrier in GF mice probably will restrict reaching of the liver bacterial metabolites to the brain [85]. Numerous remodeling experiments in GF animals confirmed that deviations of brain metabolism and behavior could be preserved through reconstitution of the gut microbial composition [1, 86].

Wong et al. found that genetically determined caspase-1 deficit in mice suppresses the anxiety-depressive like behavior and improves the motor activity and locomotor abilities, as well prevents manifestation of depressive symptoms after chronic

exposition at stressors. On the other hand, minocycline as pharmacological antagonist of caspase-1 alleviates the depressive like symptoms in wild type mice provoked by stress. Actually, both chronic stress and pharmacological inhibition of caspase-1 modify the composition of fecal microorganisms almost in the same way [3, 87].

The GF model has some limitations, which suppose that the investigators should be cautious in extrapolating the conclusions obtained in animals on people. Important is the fact that GF mice are born under aseptic conditions, such as separation from the mother via cesarean section and directly placement of the newborn in an special insulator in which the air, in which everything is sterilized, including the air, food and water. The biochemistry of brain and gut intestine is quite different [1, 81], HPA axis responses [63], in emotional, [58], social [75, 79], metabolic function, and ingestive behaviors [82] between GF animals and control animals which contain normal or pathogen-free flora obtained by colonization from the mother [8, 78]. However, up to date studies with animal model proved that the gut microbiota can influence the central nervous system in the absence of substantial changes in local or circulating cytokines or specific intestinal neurotransmitter.

It is unambiguous that bacterial products can get access to the brain via the bloodstream, they can act through the immune system via cytokine releasing by the mucosal immune cells, or through the endocrine system by triggering gut hormone release from enteroendocrine cells [9, 87]. Since GF animal models are not analogous to the development of the human brain, premature conclusions about the significance of these findings to humans should be avoided [88].

## **5. Findings from clinical, imaging and neurophysiological tests on the human brain-gut axis**

Gut to brain pathways have been explored through cortical evoked potentials (CEPs), magnetoencephalography (MEG), positron emission tomography (PET), and functional magnetic resonance imaging (fMRI) [30].

Loening-Baucke et al. applied anorectal CEP in children with constipation and encopresis and found significantly prolonged latencies of the early-onset potentials, suggesting a defect in afferent pathway conduction [89].

The perception of painful stimuli is accompanied by activation of anterior cingulate area in people in a healthy condition, as opposite to subjects suffering from IBS in which activation of left prefrontal cortex occurs probably due aberrant CNS processing [5] Subsequent research in patients with IBS also suggest that rectal hypersensitivity induced by repetitive distention of the sigmoid colon correlates significantly with increased blood flow in the thalamus and that an aberrant thalamic response to pain could be the reason for the abnormal sensitization.

In studies of Ertekin et al. and Herdman et al. conducted at different times reproducible EMG responses on the part of external anal sphincter were evoked by cortical magnetoelectric stimulation. Turnbull et al. managed to differentiate the topographic areas of the external anal sphincter and the pelvic floor muscles represented at the medial side of the primary motor brain cortex using TCMS. This representation is bilateral and shows asymmetry in some individuals [7, 30, 90–92].

## **6. Effect of interventions targeting the gut microbiota**

Known approach for registration the effects of intestinal microbes on brain function is the use self-reporting measures to determine how the brain function alters under the influence of induced from probiotics microbial proliferation.



The level of anxiety and psycho-emotional stress was reduced in human (both male and female), treated with *Lactobacillus* and *Bifidobacterium* versus persons who took control substance in a randomized placebo-control trial. However other study using different strain *Lactobacillus* does not succeed to confirm this conclusion.

But another study using a different *Lactobacillus* probiotic, failed to confirm these findings [21, 93]. The limitations in the study design including the size of the cohort, the mood of the surveyed contingent, the used assessment tools, the inter-individual differences in microbial composition and the differences between the probiotics may be the cause of the discrepancy in the results.

Another approach is to use functional MRI (fMRI) to assess changes in the human brain in response to gut microbial modulation. One study showed that chronic ingestion of a probiotic consortium altered functional brain responses in healthy women [94]. In this study, the answer to the emotional face recognition task was measured with fMRI in healthy women before and after intake of active probiotic for 4 weeks, unfermented dairy product or no treatment. Women who were treated with probiotics demonstrated diminished response to the task of emotionally recognizing in extensive brain networks, including territories, responsible for sensation and emotions. Self-assessment of anxiety and depression was not significantly different between in between the studied groups. But altered fMRI responses proposed a substantial change in response to emotional negative stimuli. Separate functional brain imaging study explored the modulatory impact of gut microbiota in subjects with mild cognitive impairment and hepatic encephalopathy through administration of non-absorbable antibacterial agent [95]. More successful coping with the cognitive task corresponded with increased subcortical activity and better frontoparietal connectivity on fMRI. Other investigation with antibiotic administration in people with the same diseases during 8 weeks also confirmed improved cognitive level and established altered serum metabolites with supposed bacterial origin [1, 26, 96].

## **7. Role of microbiota-gut-brain axis in neurological and psychiatric diseases**

Changes in the microbial environment, as a result of different stressors, are linked with alterations of barrier, motility and activation of the immune system. Perturbation of this axis lead to changes in the stress-response and behavior, which are thought to be involved in several CNS diseases, such as anxiety, depression autism, Parkinson's disease and Alzheimer's disease [97].

Neuropsychiatric comorbidity, including depression and anxiety, is common finding in patients with a functional GI disorder such as the IBS and it reaches 60% of this somatic pathology. On the other hand, IBS has also been related with changes in the gut microbiota including reduced diversity and temporal instability at the genus level. It is interesting to note that behavioral and psychological changes are often present in patients with active celiac disease, which are associated with findings of regional cerebral hypoperfusion in their brains [25, 98].

Some recent works reported for changed expression of GABA A receptor and its B subunits, responsible for the primary inhibitory brain mediation [73, 99, 100], subunits of NMDA receptors, realizing excitatory neurotransmission [101], concentration of serotonin 1A and tryptophan. Some of the above mentioned alterations corresponded with disturbed emotional behavior, which supports the interaction between microbial composition and behavior [1, 8].

In recent years evidence has emerged that neurodegenerative diseases (NDs) are strongly associated with the microbiome composition in the gut [101, 102].



## 7.1 Role of microbiota-gut-brain axis in mood disorder

A “leaky gut” is suggested to play a pathogenic role in depression. There are evidences for altered intestinal permeability in patients with mood disorder and their first degree relatives [18]. For most of the depressed patients the brain-gut axis function is impaired, including imbalance in brain neurotransmitters, decline of brain neuroplasticity, dysfunction of hypothalamic-pituitary-adrenal axis, chronic periphery inflammation and neuroinflammation, as well as gastrointestinal diseases and gut microbiota dysbiosis [103]. However, the impact of depression on the microbiota has not yet been studied [25].

Wong et al. proposed that suppression of caspase-1 plays a protective role in modulation of the interaction between representatives of the intestinal microbiota and the state of stress. They reported the importance of signals from inflammasome along the gut microbiota-inflammasome-brain axis which attribute to modification of cerebral processes, especially for manifestation of anxiety-depressive symptoms [3, 87].

Acute tryptophan depletion (ATD) in subjects suffering from depression, was preceded by bimodal emotional processing, corresponding with bimodal manifestation of the clinical symptom. It was proved in a small patient’s cohort where the alleviation of depressive symptoms occurred 24 h after ATD and the mood processing was at the better level about 5 h after depletion. The opposite processes were registered in patients who experienced worsening of the depressive symptoms [2, 104].

Serotonin is a key element of this axis, acting as a neurotransmitter in the CNS and in the ENS, located in the gut wall. This transmitter is formed in neuroendocrine cells and plays a role of paracrine hormone in the intestine. Serotonin is also an endocrine hormone which passes into the blood and bind to the platelets. Besides its system effects like maintaining the bone density and participation in metabolite processes, it performs a key connection between both ends of the gut-brain axis [105]. It is interesting that most of the serotonin is produced at the periphery predominantly in the tGI epithelium, but also in bones, breast and pancreas. Only 5% of its synthesis is realized at central level. The only difference in ways of serotonin synthesis is the use of tryptophan hydroxylase type 1 in peripheral mechanism and instead of it-type 2-in the central one [105]. The reversal process of serotonin degradation is performed with the help of monoamine oxidase and aldehyde dehydrogenase to 5HIAA both in the periphery and in the CNS [2, 96, 106].

### 7.1.1 Microbiota-gut-brain axis in major depression

Major depression disorder (MDD) is an incapacitating multifactorial psychiatric disease, which is characterized by a range of symptoms affecting both emotional and cognitive domains [107]. The hypothesis of activated peripheral blood monocytes and T lymphocytes is well known [18]. Another supposed mechanism is impaired excitation/inhibition balance that is potentially mediated by the reduced amount of GABA. The low concentration of brain-derived neurotrophic factor has been proposed as a unifying hypothesis for reduced cell numbers in frontal cortex and amygdala and also for reduced hippocampal volume. Despite the great advances in the knowledge of this disease, its etiology and pathophysiology are still not fully understood [108].

It is important that metabolites as hippurate, dimethylamine and dimethylglycine derived from the blood of patients with MDD are actually products of their intestinal microbiota [109]. Similar to findings in animal experiments in depression, limited number of studies in humans with small cohorts found changes of the gut microbiota strains [25, 110]. All this trials proposed the potential relationship between the alteration of gut microbiota composition and MDD manifestation [18].

Significant difference in the isolated bacteria from stool samples of 58 Chinese subjects, diagnosed with major depression compared to 63 healthy individuals was found. Y.

The following three main bacterial phyla are specific for the gut microbiota of depressed subjects: Firmicutes, Actinobacteria and Bacteroidetes. Depression behavior models were created through transplantation of stool samples taken from five subjects with depression into germfree mice. And vice versa, transplantation of feces from five healthy individuals did not lead to behavioral effect. Mice receiving microbiota from patients with depression showed disturbances in hippocampal gene activation and also in carbohydrate and amino-acid metabolism [16, 109]. This study provided convincing evidence that the depressive phenotype could be transferred by transplantation of the microbiota.

Kelly et al. recruited 34 patients with major depression and 33 healthy individuals with similar demographics. Plasma levels of cytokines, C-reactive protein, salivary cortisol and plasma lipopolysaccharide-binding protein were determined by ELISA, and showed alterations supporting a proinflammatory phenotype linked with depression. Depression was associated with decreased gut-microbiota richness and diversity. A fecal microbiota transplant was prepared from a subgroup of patients with depression or from healthy individuals and transferred by oral gavage to a microbiota-deficient rat model [114].

But further research in larger samples and unified MDD populations is required to confirm whether disturbances in gut microbiota have a causative role for the onset of MDD.

## **7.2 Microbiota-gut-brain axis in autistic spectrum disorders (ASD)**

During the early onset of this developmental disorder an autistic enterocolitis and changes in intestinal permeability occur [111]. Moreover, urinary metabolic phenotyping has determined biochemical changes that were consistent with abnormalities in the composition of the gut microbiota, found in autistic children.

Recent studies suggest that changes in antigenic load due to the impairment of gut barrier function is triggering factor for clinical manifestation of autism [112]. Desbonnet et al. are the first scientists who found that microbiota are crucial for the programming and presentation of distinct normal social behaviors, including social motivation and preference for social novelty, while also being important regulators of repetitive behaviors. Taking into account that these aspects of behavior are impaired in neurodevelopmental disorders such as schizophrenia and autism [5] and with a male preponderance, these data extend our knowledge regarding the genesis of neurodevelopmental disorders of altered sociability. A better understanding of the underlying mechanisms of these social deficits, which may include modulation of immune cell cytokines release, changes in vagal nerve activity and neuroendocrine function, can help for developing of innovative and more effective strategies in managing of these social disturbances [76].

A study of Kang et al. revealed less abundance of Bifidobacteria species and the mucolytic bacterium *Akkermansia muciniphila* in children with autism [114–116]. Other experiment showed less diverse gut microbial composition with lower levels of *Prevotella*, *Coprococcus*, and unclassified *Veillonellaceae* in ASD [117]. Another study showed a significant increase in several mucosa-associated Clostridiales, whereas a decrease in Dorea, Blautia and Sutterella was seen in AUTISM-FGID [118].

## **7.3 Microbiota-gut-brain axis in Alzheimer disease**

Alzheimer disease is a progressive neurodegenerative illness associated with accumulation of proteinaceous misfolded amyloid- $\beta$  (Ab) fibrils and oligomers,

together with neurofibrillary tangles consisting of hyperphosphorylated tau protein in the cerebral cortex and other brain regions [118]. Recent research indicates that alterations of the gut microbiome could activate proinflammatory cytokines and increase intestinal permeability, leading to insulin resistance, which has also been found in AD [119].

Bacterial representatives of the gut microbiome excrete lipopolysaccharides (LPSs) and amyloids. These products lead to forceful pro-inflammatory and innate-immune effects, activate the system. Following enhanced amyloid aggregation, as well secondary degeneration occur, which are typical signs of AD, together with impaired cleansing mechanisms of A $\beta$  peptide [17, 120, 121]. It has been suggested that diet and specific nutrients could alter the composition of the intestinal microbiota and might influence the production or aggregation of amyloid proteins [29, 114, 122].

#### 7.4 Microbiota-gut-brain axis in Parkinson disease and its prodromes

Currently it is well established that Parkinson's disease (PD) is not a pure movement disorder of the CNS but also a gastrointestinal disease [115–117], which affects the ENS [123–125]. The main premotor PD symptoms include rapid eye movement sleep behavior disorder, hyposmia, constipation and depression [126].

Rapid eye movement (REM) sleep behavior disorder (RBD) is a parasomnia which results from the loss of physiological motor inhibition and is manifested with abnormal behavior during REM sleep. That disorder leads to varying degrees of complex motor activity which ranges from sleep talking to violent dream enacting behaviors potentially harmful for the subject or bed partner [127, 133].

In their study Heintz-Buschart et al. revealed differential abundances of gut microbial taxa (such as *Akkermansia*) in Parkinson disease (PD) and its prodromal state idiopathic REM sleep behavior disorder compared to healthy controls. The majority (about 80%) of the differential gut strains in patients with PD are very similar to those in subjects with idiopathic REM sleep behavior disorder. Most common are *Anaerotruncus* and *Bacteroides*, which correspond to non-motor symptoms of the disorders. Metagenomic sequencing of specific microbial samples allows the genomic reconstruction [23, 128]. Other studies registered reduction of microorganisms as *Faecalibacterium*, *Coprococcus*, *Blautia*, *Prevotella* and *Prevotellaceae* in gut of subjects, suffering from PD. These alterations are non-disease specific at a lower taxonomic level, for example at phylum stage, but at higher taxonomic level as genus or species, was registered some overlap between alpha synucleinopathies such as PD and multisystem atrophy (MSA) [3, 102].

It has been shown that PD patients with RBD exhibit much higher frequencies of phosphorylated  $\alpha$ syn pathology in the colon and in the skin compared to PD patients without RBD [129]. Also, idiopathic RBD subjects exhibit marked pathology in the sympathetic and parasympathetic nervous system, but a relatively intact dopamine system [130].

For *Prevotella* such reduction has also been observed in RBD patients. Based on the attributed functional properties of these bacteria, such alterations could affect gut barrier integrity, short-chain fatty acid (SCFA) production, and inflammation. This would be in line with reports of a leaky gut and reduced levels of SCFAs and lipopolysaccharide binding protein in PD patients.

An interesting link between gut microbiota and  $\alpha$ syn pathology could be cross-seeding of amyloid pathology induced by bacterial amyloid proteins such as curli.

So far, human microbiome studies in PD have been carried out exclusively in medicated patients, except for one study that included also idiopathic RBD patients



[131]. While the PD associated microbiome alterations have been confirmed in drug adjusted analyses, confounding effects which could be result of COMT inhibitors intake cannot be excluded. Another potential confounder is colonic dysmotility, which may independently alter microbiota composition [132, 133].

Thus, observed brain and behavioral changes may be mediated by the absence of intestinal microbes directly or indirectly through one or more of the non-brain-related alterations. The latest data show that the intrauterine environment is not sterile, and it can even be supposed that microbial metabolites of the intestine from the maternal microbes of the intestine may have an effect on the development of the fetal brain [75]. The altered signaling of the cecum to the brain secondary to the massive cecal dilation associated with this model may alter the development of the brain regions that process this input [88].

## 8. Discussion

The gut microbiota has co-evolved with its host for millennia and influences positively many functions of the host organism, as digestion, production of nutrients, detoxification, defense against pathogens and immune regulations [2, 3, 123].

As a key component of the gut brain, gut microbiota influences the development and maturation of the HPA axis [134], affects the development and function of the immune system [135], regulates the blood-brain barrier [136], modulates the synthesis and recognition of neurotransmitters [73], regulates neurogenesis, formation of myelination [137], and supports the development and function of the brain [78]. Microbiota-gut-brain axis plays a crucial role for manifestation of mental disorders [103].

Following the development of gut microbiota, the scientists not only focus on the top-down effects of the brain-gut axis (from brain to gut), but they also devote special attention to the bottom-up influences (from gut to brain) [138]. Alterations of the “gut brain” as pathological changes of intestinal microbiota affect the brain activity and have an impact on behavior. In turn, the emerging brain changes provide feedback on the gut. Uniting the brain and the colon, the brain as targeting gut microbiota organ is becoming a key trend in neuroscience and reliable field for successful management of neuropsychological disorders [11, 103].

Treatment with antidepressants has achieved a significant improvement from the introduction of selective serotonin re-uptake inhibitors and rather the introduced serotonin and noradrenaline re-uptake inhibitors, however, there are still outstanding clinical requirements for the treatment of depression, and better therapeutic strategies are needed, especially with regard to the treatment of depressive cure and additional comorbid painful physical conditions such as GI discomfort [5]. There are confirmations for intestinal microbe changes in patients suffering from major depression [114, 139], as well as in IBS. Considering the serious evidence from laboratory animal models in which the stress affects brain-gut-microbial axis, this area requires more research in humans. In addition to the effects on the immune system, probiotics have also been shown to improve carbohydrate malabsorption [140], which in turn is associated with both early signs of depression and reduced levels of tryptophan [141].

There is a reasonable assumption that probiotic treatment can produce a beneficial effect on mood by raising serotonin precursor levels, tryptophan, and hence increasing serotonin availability [5]. Despite these promising initial findings on microbiota and stress-related disorders, there is a relative lack of research among healthy individuals linking the composition and function of the microbes inhabiting the human intestine and levels of chronic stress or susceptibility to acute stress [26].



Studies in animal models are crucial for guiding research on brain-gut microbiome-axis in humans, as the impact of microbiota on specific brain regions and aspects of animal behavior will help in the selection of tasks for cognitive assessment. Such studies will also be useful in identifying which bacteria may be of particular importance. For example, in rodent models, a specific strain of *Bifidobacterium longum* was found to alter cognition, [142], as well as stress-related behavior and physiology, and a similar effect profile was subsequently observed in people given this strain [26, 143].

Recent research indicates that the gut microbiota is associated with health in the elderly, with those in long-term care having a less diverse microbiota than those living in the community [144]. Even in healthy aging, some aspects of cognition could be deteriorated. Despite the growing interest in this problem, there is still lack of sufficient studies, especially of long-term longitudinal research examining changes in the human gut microbiota with aging. The high inter-individual variation in the gut microbiota also impedes interpretation. Such research efforts should occur in the context of rapid acceleration of genetic sequencing technologies for better characterizing of the gut microbiota [26, 145].

We are witnesses of extraordinary merging of research approaches in different areas of psychiatry, gastroenterology and neurology which significantly improve our understanding of neuropsychiatric diseases and more clearly explain the close relationship between GI and mood disorders. As a result the therapeutic strategies in some mental illnesses significantly advanced. For example, IBS, recognized as linked with psychosocial and GI disorders [6, 146] and often accompanied by depressive symptoms [147, 148] has improved since introduction of an interdisciplinary approach [5]. Although the brain and gut are organs with quite different functions at first glance, the emerging part of the scientific sources provides proofs for their synergy along the “brain and gut axis” and suppose that not only the brain may affect the intestinal function but also the gut, both by direct and by indirect mechanisms can cause alterations in CNS [6, 149], and in stress-related disorders such as depression [5].

It is not known whether the observed changes in the microbiome play a causal role in the development of the intestinal pathology in PD or whether they are a consequence of the altered intestinal function. However, observations that motor symptoms, neuroinflammation, asyne pathology and intestinal motility may be modulated by manipulation of the gut microbes in transgenic asyne-overexpressing mice suggest that such causative effects are possible [150, 151].

In order to establish which mechanisms connect microbe alterations and PD, such studies should use a multiomics approach, including meta-genomic, metatranscriptional and metabolomic assays, in combination with assessment of host factors such as intestinal biopsy, permeability studies, cytokine levels and host genotype. For this purpose multi-center consortia need to cooperate to ensure a sufficient cohort size and standardized methodology [132].

A fuller understanding of the human “hologenome,” of human microbial ecosystems and their secretory products should provide a deeper insight into their contribution to age-related neurological diseases associated with amyloidogenesis, CNS inflammation and progressive neurodegeneration [120].

It is suggested that modulating the gut microbiome through specific nutritional interventions and the use of prebiotics and probiotics might represent an effective strategy to reduce the level of chronic inflammation and Ab associated with AD, possibly preventing or ameliorating AD symptoms [29].

A deeper understanding of how psychological development and social and cultural factors affect the brain-gut-microbiome axis will contextualize the role of this axis in humans and give a light on the necessary psychological interventions that

will improve the health of the brain-gut-microbiome axis. Interventions apparently aimed at alleviating disorders in a part of the brain-intestinal-microbial axis (e.g., depression psychotherapy) may still affect other parts of the axis (e.g., microbial composition and function) and functional GI disorders such as IBS are disorder of the axis, not an isolated problem of both psychology and gastrointestinal function. Discipline psychology should be aware of these interactions in order to help create a future research program in this emerging research area [26, 152].

## 9. Conclusion

The gut microbiota influences the brain biochemistry and hence—the behavior irrespective of the autonomic nervous system, specific GI neurotransmitters, or inflammation. The intestinal commensals communicate with the human body via immune, endocrine and neural mechanism. These functional pathways are part of the microbiota- gut-brain-axis and according to preclinical evidence the gut microbes can recruit the above mentioned bidirectional communication relationship to modulate not only the brain development and functioning, but also our behavior. Disruption of gut-brain axis function is associated with alterations in the stress response and might contribute to neuropsychiatric diseases as mood disorder, ASD, REM sleep behavior disorder, Parkinson disease, Alzheimer disease and other mental conditions. Exploring the interaction of gut microbes and human brain will not only allow us to better understand the pathogenesis of neuropsychiatric disorders, but will also provide us new opportunities for the design of novel immuno- or microbe-based therapies.

## Conflict of interest

No.

## Author details

Valentina Ignatova  
Clinic of Neurology, Multiprofile Hospital of Active Treatment, National Heart Hospital, Sofia, Bulgaria

\*Address all correspondence to: [valyaig@abv.bg](mailto:valyaig@abv.bg)

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