REVIEW

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# The gut microbiota in neuropsychiatric disorders

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The purpose of this review is to summarize current knowledge about the gut microbiota in neuropsychiatric disorders. It is estimated that the human gut is colonized by up to $10^{18}$ microorganisms, mostly anaerobic bacteria. The gut microbiome is responsible for multiple functions, e.g. tightness of the intestine barrier, digestion and absorption. The correlation between gut dysbiosis and development of psychiatric, autoimmune and allergic diseases as well as bidirectional communication between brain and gut microflora have been shown. Recent findings suggest that specific bacteria can be involved in the development of clinical conditions, such as Autism Spectrum Disorders, depression and schizophrenia, and microbiota may be a target for therapeutic intervention providing novel treatment strategies.

Key words: gut, microbiota, neuropsychiatric disorders

## INTRODUCTION

The gut microbiota is composed of thousands of bacteria species weighting together up to 2 kg (Thomas et al. 2015). It is estimated that the human gut is occupied with up to $10^{18}$ microorganisms: bacteria ($10^{14}$, mostly anaerobic), viruses, yeasts, and fungi (Turroni et al. 2008), some of them are unculturable or uncharacterized (Turroni et al. 2008). The intestinal microbiome contains approximately 150 times more unique genes than the human genome (Qin et al. 2010) and the intestinal microflora represents over 200,000 to 1,000,000 bacterial genes (Thomas et al. 2015). The microbiota can be described as metabolic 'organ' representing functions that humans have not evolved on their own (Backhed et al. 2004, Bocci 1992). It can communicate with the host, repair itself through self-replication and perform a lot of functions: consuming, mediating chemical transformations, storing and redistributing energy (Backhed et al. 2005).

Microbiota represent an important protection system of the gastrointestinal (GI) tract against harmful pathogens and external factors (Mangiola et al. 2016). Bacteria living in the human intestine achieve the highest documented cell concentration for any ecosystem, $10^{11}$-$10^{12}$ per mL (Hu et al. 2016, Hugenholtz et al. 1998). The most common phyla in the small intestine are Firmicutes and Bacteroidetes, whereas Proteobacteria, Actinobacteria, Fusobacteria, Archea and Verrucomicrobia are represented in smaller quantities (Grenham et al. 2011, Sartor 2008).

The relationship between human and gut microbiota was described as 'commensal' (one partner benefits when another is unaffected), which shows that our knowledge is insufficient (Backhed et al. 2005). The gut microbiota is responsible for maturation of the immune system (Kau et al. 2011) in particular of GALT (gut-associated lymphoid tissue) through stimulation of local and systemic immune responses (Nell et al. 2010). The continuous stimulation of the immune system by intestinal bacteria generates a "low-grade physiological inflammation", which is a rapid and effective defence against pathogens (Fond et al. 2015, Rakoff-Nahoum et al. 2004). The microbiota communicates with the immune system and *vice versa* (Elson and Alexander 2015) thus dysbiosis defined as shift of microbial composition and beneficial

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functions (Fond et al. 2015) can result in immune-mediated inflammatory disorders, such as celiac disease (Elson and Alexander 2015).

Microflora is responsible for digestion of meals and drugs, absorption and distribution of fat (Backhed et al. 2004, Serino et al. 2012). It is involved in vitamin K synthesis (Backhed et al. 2005), the production of mucus by secreting the short chain fatty acids (SCFAs). It causes epithelial regeneration consequently increasing the tightness of the intestine barrier (Burger-van Paassen et al. 2009), and stimulation the angiogenesis (Stappenbeck et al. 2002).

The gut microbiota is relatively stable after the age of 3 years and tends to lose diversity in the elderly (Salazar et al. 2014). Microbial colonization begins shortly after birth, but some studies show the existence of microorganisms in placenta, amniotic fluid, umbilical cord blood, and meconium (Aagaard et al. 2014, DiGiulio 2012, Moles et al. 2013). In the newborns the gut is colonized by facultative anaerobes which create a more suitable environment for the strict anaerobes (Fanaro et al. 2003). It is accepted that the gold standard microbiota in infants is that of full-term vaginally delivered breast-fed babies (Salazar et al. 2014). Consequently the composition of microflora in this stage of life is influenced by many factors, e.g. type of feeding, delivery mode, and use of antibiotics (Penders et al. 2006). The intestine of children fed by breast milk is dominated by Proteobacteria (Fan et al. 2014). It was observed that breast fed infants have higher amounts of bifidobacteria, *Bacteroides spp.*, more varied microbiota and a lower level of potential pathogens than formula-fed babies (Bezirtzoglou et al. 2011, Fallani et al. 2010). Weaning stimulates growth of Bacteroidetes and Firmicutes, and decreases growth of Bifidobacteria and Proteobacteria (Fallani et al. 2011). The induction of solid foods shifts towards bacteria typical for 'adult' microbiota (Palmer et al. 2007). This type of gut microflora is dominated by Bacteroidetes and Firmicutes (Arumugam et al. 2011). The 'adult-like' intestinal microbiota in the absence of significant ecological stressors represents a high stability and homeostasis (Salazar et al. 2014). Intestinal microbiome diversity is higher among infants than adults (Koenig et al. 2011, Kurokawa et al. 2007). In the elderly, the microbiota represents reduced species diversity causing it less resistant to major fluctuations in response to environmental factors. These changes induce decrease of beneficial bacteria and availability of total SCFA, increase of facultative anaerobes (Salazar et al. 2013, 2014). It was shown, using a mouse model, that adolescence and early adulthood are the critical periods when perturbations in the intestinal microflora and dysregulation of microbiota-gut-brain axis can influence brain development and animal behavior (Desbonnet et al. 2015). These changes can lead to altered cognitive functions and anxious phenotypes in adulthood.

Until recently the relationship between gut microflora and health was largely unknown, mainly due to the lack of methods to study unculturable microorganisms (Salazar et al. 2014). Currently, two methods are commonly used to investigate the relationships between diet, gut microbiome and gut-brain axis: metagenomic (involving culture-independent methods for describing microorganisms) and gnotobiotic (the raising of animals in germ-free conditions at various stages of life and different microflora compositions) (Kau et al. 2011, Turnbaugh et al. 2009, Wikoff et al. 2009).

Our knowledge about the composition and function of intestinal microflora is still unsatisfying (Arumugam et al. 2011) because of dramatic changes in cultural traditions, the growth of population, social and economic status, and agriculture affecting the diet modification. Understanding how these dietary changes affect human gut microflora represents an area of scientific need and challenge (Kau et al. 2011). Advances in modern life such as use of antibiotics, vaccination, high-calorie diet and cleaning products bring significant changes (Flint 2012). Furthermore, the personal profile of the microbiome is continually influenced and changed by diet, genetics, sex and age (Jumpertz et al. 2011, Kau et al. 2011). The microbiota profile might be a valuable representation of the personal environmental history: its dynamic nature and diversity determined to date extends far beyond what researchers expected (Zhou and Foster 2015).

The main diseases investigated in the context of a correlation between gut dysbiosis and development of diseases are: inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), Crohn's disease, autoimmune and allergic diseases, obesity, neurological and psychiatric disorders (Andoh and Fujiyama 2006, Dash et al. 2015, Elson and Alexander 2015, Fond et al. 2015, Garrett et al. 2007, Ley et al. 2005, Macdonald and Monteleone 2005, Macpherson and Harris 2004, Mangiola et al. 2016, Mayer et al. 2014, Principi and Esposito 2016, Serino et al. 2012, Turnbaugh et al. 2006, Zhou and Foster 2015).

## The neuronal gut-brain communication in neuropsychiatric disorders

Bidirectional communication between brain and gut microflora has been reported by many authors (Critchfield et al. 2011, DellaGioia and Hannestad 2010, Forsythe et al. 2010, Grenham et al. 2011, Mayer et al. 2014, Messaoudi et al. 2011). Not only physical and psychological stressors may affect the composition and metabolic activity of the gut microbiota, but it is also suggested that

the intestinal microbiome affects the brain by the humoral and neuronal mechanisms with particular attention to the vagus nerve (Dash et al. 2015). Signals from the brain may influence sensory, motor, and secretory modalities of the GI tract, and signals from the GI tract influence brain functions, however, the exact mechanisms are not well understood (O'Mahony et al. 2011, Principi and Esposito 2016).

The existing brain-gut axis is further supported by using antibiotics and usually probiotics (defined as living organisms, which taken in appropriate amounts cause health benefits to the host (Bravo et al. 2012) as a treatment for many diseases. Administration of probiotics as food ingredients or supplements can be beneficial for the host. They consist primarily of lactic acid-producing bacteria, such as lactobacilli, lactococci, bifidobacteria and yeasts (e.g. *Saccharomyces boulardii*) (Critchfield et al. 2011). Probiotics restored gut physiology in stress caused by neonatal maternal separation model by regulating the interaction between mucosa and bacteria and reducing hypothalamic–pituitary–adrenal axis (HPA) hyperreactivity in rats (Gareau et al. 2007).

Diet modification of gut microbiota composition may affect the inflammatory mechanisms (Cani et al. 2007) and damage the intestinal barrier and consequently facilitate the inflow of harmful substances like bacterial metabolites from gut to lumen (de La Serre et al. 2015, Sen et al. 2017). It was observed that high-sugar diet induces gut inflammation and alters vagal gut-brain communication (Sen et al. 2017), as well as high-fat diet causing vagal remodeling can be the reason for alterations in neuronal signaling (Vaughn et al. 2017). Interestingly, it was shown in rats that interferences of vagal afferent signaling are able to cause obesity in a diet-induced models (de Lartigue et al. 2012, Sen et al. 2017), thus, dysregulation of vagal communication between gut and brain is hypothesized to play a role in pathogenesis of obesity and related diseases (Sen et al. 2017). Moreover, microbiota signals affecting the brain can be changed by vagal afferents (Vaughn et al. 2017, Wang et al. 2002). These authors found that eating too much sugar can cause gut inflammation or diminish gut permeability, which combined with dysbiosis may effect endotoxemia (defined as too much circulating lipopolysaccharides, LPS) (Sen et al. 2017).

LPS, also known as lipoglycans or endotoxins, are found in the outer membrane of Gram-negative bacteria, which elicit strong immune responses in animals. They are the markers showing brain-gut microflora bidirectional communication (Bengmark 2013). Antibiotic reduction of luminal LPS concentration attenuates the HPA axis stress response and increases hypothalamic expression of pro-inflammatory cytokines, such as tumour necrosis factor-α (TNF-α), interleukin 6 (IL-6), IL-1β (Ait-Belgnaoui et al. 2012, Theoharides et al. 2013). Even low doses of LPS may cause fatigue, anorexia, depressed mood and apathy (DellaGioia and Hannestad 2010) characteristic of depressive disorder (Dunn and Swiergiel 2005), and inflammation-related states such as autoimmune disease (Johnson et al. 2005). LPS are a potent proinflammatory factors able to alter neuronal activity in the limbic system (e.g. it can increase activity of amygdala) (Haba et al. 2012), and to activate vagal afferent neurons (de Lartigue et al. 2012).

Microbial metabolites are important immunomodulators (Qiu et al. 2012). SCFAs are the end-products of microbial fermentation of macronutrients and not constitutively digested by humans. The missing enzymes are delivered by bacteria, therefore SCFAs are good markers of intestinal microflora composition (Kau et al. 2011), e.g. *Clostridia spp.* and *Bacteroides spp.* are important SCFA producers. Major effects of these compounds are the modification of mitochondrial functions (by the citric acid cycle, carnitine metabolism or epigenetic modulation of genes controlling brain function) (Principi and Esposito 2016). Gut microflora can also influence the central nervous system (CNS) by endocrine pathway (corticotropin-releasing factor, CRF) (Rodino-Janeiro et al. 2015) or by modification blood-brain barrier (BBB) (Braniste et al. 2014). There were observed higher levels of these components in the "leaky gut syndrome (LGS, the increased gut permeability) (Critchfield et al. 2011).

The nucleus of the solitary tract (NTS) and dorsal motor nucleus of the vagus (DMV) are the first stations receiving information about nutrition status from the GI tract (Rogers and McCann 1993). It was shown that a high-fat diet, by changing the gut microbiota composition, is able to cause endotoxemia and neuronal damage to the NTS and DMV. This effect includes activation of microglia and vagal remodeling in these regions (Vaughn et al. 2017). Effective treatment by minocycline in rats resulted in normalization of gut microbiota composition and protection against neuronal damage (Vaughn et al. 2017).

## Autism spectrum disorders

Autism spectrum disorders (ASD) are defined by impairments in verbal and non-verbal communication, social interactions, decreased verbal skills, repetitive behavior, insistence to routines, and unusual response to sensory stimuli (Critchfield et al. 2011, Williams et al. 2011). Data from the Center of Disease Control in the USA indicate that as many as 1/80 children have ASD (Williams 2012) and the diagnosis of ASD has increased dramatically over the last years (King and Bearman 2011). Among the potential causes of the rising incidence are

broadening of diagnostic criteria and greater awareness among health care professionals (MacFabe et al. 2007), however, one cannot rule out other causes. The prevalence of ASD is between four and eight times higher in males than in females (Bertrand et al. 2001). The lack of knowledge on distinct pathogenesis of ASD and specific biomarkers are important obstacles in developing effective treatments (Theoharides et al. 2013).

Possible risk factors for developing ASD are prenatal exposures to thalidomide, valproic acid, and ethanol (Arndt et al. 2005). Although some parents report an association between abdominal discomfort in their children (e.g. constipation, colic, gastroesophageal reflux and diarrhea) and the onset of autistic symptoms (MacFabe et al. 2007), the prevalence of GI symptoms in autistic children is not precisely defined and ranges between 9 to 70% (Buie et al. 2010). Probably the lower scores are obtained in population studies, whereas the higher scores are defined in specialized GI clinics. Moreover, in these children a high frequency of GI dysfunction is usually associated with increased irritability, aggressive behavior, tantrums, and sleep disturbances (Critchfield et al. 2011).

Some authors correlate ASD symptoms with immune dysfunction and increased inflammatory markers. Proinflammatory cytokines: IL-6, TNF and monocyte chemotactic protein 1 (MCP-1) were found in cerebrospinal fluid of ASD patients (Li et al. 2009b, Onore et al. 2012, Theoharides et al. 2012, Vargas et al. 2005). Methods such as histology, immunochemistry and flow cytometry revealed infiltration of immune cells (e.g. lymphocytes with proinflammatory phenotype CD3+ TNFα+ cells or CD3+ IFNγ+ cells, monocytes, NK cells) in the GI tract of autistic children (Ashwood and Wakefield 2006, Furlano et al. 2001, Torrente et al. 2002).

It is documented that higher serum LPS levels occur in autistic patients with worse social interactions in the comparison to healthy controls (Emanuele et al. 2010). LPS levels correspond to increased IL-1β and IL-6 levels, responsible for inflammatory and immune dysregulation in autism (Emanuele et al. 2010). LGS is responsible for bacteria migration through the intestinal barrier to blood and increase of LPS serum levels in humans (Erridge et al. 2007). Bacterial components in the blood may release inflammatory responses and consequently affect neuronal signaling (Critchfield et al. 2011, Emanuele et al. 2010).

Diet is also thought to influence children with ASD, e.g. a Western diet, depending on inflammatory state, can cause anxiety-like behavior and memory problems (Ohland et al. 2013). The high prevalence of ASD in India (approximately 2 million) may be correlated with typical Indian carbohydrate-rich diet and consequently predominance with of genus Prevotella and Megasphaera (Bhute et al. 2016, Pulikkan et al. 2018). The Veillonellaceae family, which were increased in children with ASD in comparison to healthy controls, was also associated with a carbohydrate-rich diet (including gluten) (Ercolini et al. 2015, Pulikkan et al. 2018). These findings confirm the thesis suggesting that diet induced dysbiosis may be important in pathomechanism of ASD.

Autistic children are characterized by higher levels of fermentation products than corresponding healthy controls (Wang et al. 2012). Phenols, amines, ammonia can be toxic to the large bowel suggesting that gut microflora and intestinal barrier are important in the pathogenesis of ASD (Nowak and Libudzisz 2006). Propionic acid (PPA) is the end-product of enteric bacteria in the intestine (Shultz et al. 2008) and a common preservative added to refined wheat and dairy products (Brock and Buckel 2004). PPA is able to affect autistic behaviors (Critchfield et al. 2011), e.g. higher occurrence of autistic symptoms shortly after the eating of refined wheat and dairy were observed (MacFabe et al. 2007). The authors report a significant improvement in child's behavior following the elimination of these products from the diet, especially in speech and communication skills, lower hyperactivity, better focusing and night sleep with concurrent resolution of GI symptoms (Jyonouchi et al. 2002). Experimental intraventricular administration of PPA in a rat model demonstrated changes in animal behavior (MacFabe et al. 2007, Shultz et al. 2008). PPA might be responsible for behavioral, neuropathological and biochemical abnormalities observed in autism and might represent a connection factor between dietary or derived metabolites along with genetic predisposition, and subsequent symptoms of ASD (MacFabe et al. 2007, Wajner et al. 2004).

Differences in gut microbiota between children with autism and healthy controls were described in affected children: 10 times higher amount and diversity of *Clostridium spp.* (Finegold et al. 2002, Parracho et al. 2005, Song et al. 2004), changed Firmicutes: Bacteroides ratio (the lower levels of Firmicutes and higher of Bacteroides) (Finegold et al. 2010), the increase of: Bacteroidetes, Alcaligenaceae family, *Lactobacillus* and *Sutterella* genera, and the decreased levels of *Prevotella spp.* and *Bifidobacterium spp.* (Adams et al. 2011, Finegold et al. 2010, Kang et al. 2013). It should be noted that Bacteroidetes produce PPA and other SCFAs, and experimental injection of any SCFA into cerebral ventricles of rats caused typical autistic behavior (MacFabe et al. 2007). Williams et al. (2011) observed contradictory decreased levels of Bacteroidetes and increased Firmicutes/Bacteroides ratio. The explanation for this may be using different materials: most authors analyzed the fecal samples, whereas in this particular study authors investigated ileal and cecal biopsies materials.

Short-term improvement was observed after vancomycin treatment in eight out of eleven children with regressive, onset autism, but it largely waned at follow-up (Critchfield et al. 2011, Sandler et al. 2000). Although not suggesting the usefulness of therapy, these results support a possible gut microflora-brain connection.

Treatment of mice exhibiting autistic behaviors by *Bacteroides fragilis* repaired the intestinal permeability by tight junction protein expression and production of IL-6 (Hsiao et al. 2013). Using probiotics in treatment of autistic children can improve their behavior, but it needs to be established in well-controlled trials with sufficient group sizes (Critchfield et al. 2011).

Although there is evidence that gut dysbiosis is involved in pathogenesis of ASD, some studies did not show differences in the composition of gut microflora between autistic children and healthy controls (Gondalia et al. 2012). The principal limitations of the studies include the number of patients, the differences among groups (diverse lifestyles, environmental risk factors, habits and diet intake) (Emanuele et al. 2010), sometimes not properly examined treatment strategies, e.g. fecal microbiota transplantation (Evrensel and Ceylan 2016). Despite these limitations proved changes in gut microflora composition, modifications of immunological markers and intestinal barrier provide a clue for future treatments.

## Depression and anxiety

Depression is characterized by low mood, low self-esteem and loss of interest in normally enjoyable activities (Kessler et al. 1996, Naseribafrouei et al. 2014), and its diagnosis requires the occurrence minimum of five symptoms from the APA 2000 list (DellaGioia and Hannestad 2010), whereas anxiety is described as a common form of mood disorder with nervous, endocrinal, and immunological pathogenesis (Wang and Kasper 2014). A severe bout of depression may lead to death, not only by committing suicide (Dome et al. 2009). Scientist predict that one of six persons will experience at least one episode of depression during their lifetime (Kessler et al. 2005).

It is hypothesized that depression may result from neuroimmunological dysregulation (Dantzer et al. 2008, Wang and Kasper 2014). The direct correlation between gut microbiota and depression remains unclear, but indirect evidences including inflammatory, stress or signaling pathways were described (Dinan and Cryan 2013, Foster and McVey Neufeld 2013). Clinically minocycline (second generation tetracycline) was successfully tested as a treatment for depression (Soczynska et al. 2012).

In rodents acute stress causes increased gut permeability (Julio-Pieper et al. 2014), and germ-free (GF) mice exhibit reduced anxiety and increased motor activity in a comparison to specific pathogen free (SPF) mice (Neufeld et al. 2011). There is some evidence for the reverse situation, when the increased intestinal permeability affects psychological stress: the challenge with *Citrobacter rodentium* in mice caused anxiety-like and increased risk assessment behavior (Julio-Pieper et al. 2014), supporting the correlation between anxiety-like behavior and gut microbiota composition.

Modifications of traditional lifestyles, among which diet is especially mentioned, were correlated with many mental disorders, mainly depression (Hidaka 2012, Selhub et al. 2014). Population studies showed that "traditional dietary practice" was related to lower risk of depression and anxiety, e.g. typical for Japanese fermented soy products (Nanri et al. 2010). These findings were confirmed in animals studies: mice fed by beef presented higher gut microbial diversity, better reference memory and decreased anxiety in comparison to chow-fed ones (Li et al. 2009a). Moreover, drinking water enriched with *Lactobacillus helveticus* and *Bifidobacterium longum* can increase nerve cell resiliency during experimental physiological stress in rats (Girard et al. 2009).

Suggestions that depression is characterized by cell-mediated immune activation and inflammation were published by Maes et al. already in early 1990-ties (Maes et al. 1990, 1991, Maes 1993). Investigators have observed that depression coexist with other inflammatory diseases (rheumatic diseases, inflammatory bowel disease, multiple sclerosis) (Howren et al. 2009, Karakula-Juchnowicz et al. 2014) and abnormalities in serum cytokines correlate with depression (Dantzer et al. 2008). Higher levels of proinflammatory IL-6 and TNF-α were found in affected patients as compared to healthy controls (Bremmer et al. 2008, Dome et al. 2009, Dowlati et al. 2010, Hestad et al. 2003, Sluzewska et al. 1995, Zorrilla et al. 2001). Moreover, successful antidepressant treatment for major depressive disorder reduced serum cytokine levels of IL-1β and IL-6 (Hannestad et al. 2011).

Composition of the gut microflora and its impact on symptoms of depression was analyzed (Dash et al. 2015, Dinan and Cryan 2013, Mayer et al. 2014, Naseribafrouei et al. 2014) and three general mechanisms have been proposed: 1) through inflammation directly, 2) through the HPA, or 3) through interference with neurotransmitter signaling (DellaGioia and Hannestad 2010, Foster and McVey Neufeld 2013). Importantly, abnormal activities of the HPA axis have been diagnosed in patients with various mental disorders, such as schizophrenia (Walker and Diforio 1997), depression (Holtzheimer

and Nemeroff 2006), posttraumatic stress disorder (de Kloet et al. 2005).

As mentioned above, LPS may be an important factor contributing to psychiatric disorders (Berk et al. 2013, Qin et al. 2007). Endotoxin administration to healthy male volunteers caused response with dose-related elevations in body temperature and heart rate, increases in plasma (IL-6, IL-10, TNF-α and IL-1 receptor antagonist IL-1Ra), salivary and plasma cortisol, plasma norepinephrine, and these changes were accompanied by dose-related decreased mood, increased anxiety levels and modulations of emotional memory (Grigoleit et al. 2011). IgA- and IgM- mediated inflammatory responses to LPS have been also shown to be elevated in patients with depression (Maes 2011).

Some authors observed differences in gut microbiota in patients with depression compared to healthy controls: increased levels of Enterobacteriaceae family and *Alistipes spp*. (Jiang et al. 2015, Naseribafrouei et al. 2014), which can be modified by changes in diet (Naseribafrouei et al. 2014). Interestingly, *Alistipes spp.* are overrepresented in irritable bowel syndrome (IBS) (Saulnier et al. 2011), suggesting a possible common mechanisms (Zhou and Foster 2015). A higher Firmicutes: Bacteroides ratio in patients with IBS correlated with clinically overt anxiety and depression (Jeffery et al. 2012), thus supporting a relationship between depression and gut microbiota composition. Conversely, a negative correlation was shown between the expression of *Faecalibacterium spp*. and Bacteroidetes, and the occurrence of depression (Jiang et al. 2015, Naseribafrouei et al. 2014). Similarly to obese patients (Ley et al. 2006) these relationships may provide link between obesity and depression.

Experimental studies performed on animals investigating the role of gut microbiota composition in anxiety, demonstrated increased stress-reactivity in GF mice (Sudo et al. 2004). Interestingly, GF mice are smaller and show higher anxiety levels than matched SPF ones (Backhed et al. 2004, Luna and Foster 2015). GF mice showed increased anxiety-like behaviors in the open-field and marble-burying tests than specific pathogen free animals and mono-association of GF mice with *Blautia coccoides* reduced anxiety-like behaviors (Nishino et al. 2013). The effect is bidirectional since the murine gut microbiota can influence emotions, and stress and anxiety promote the growth of *Odoribacter spp*., *Alistipes spp.* and family Coriobacteriaceae (Bangsgaard Bendtsen et al. 2012). Separation of rats from their mother showed that neonatal stress induces long-term modifications in the intestinal microbiota diversity and composition (Garcia-Rodenas et al. 2006, O'Mahony et al. 2009), e.g. causes decrease of *Verrucobacteria* and increase of *Clostridium spp.* (Aguilera et al. 2013), but feeding rats with *B. infantis* 35624 normalized immune response, behavior and noradrenaline concentrations in the brain stem (Desbonnet et al. 2010).

GABA can be synthesized by intestinal bacteria: *Lactobacillus brevis* and *Bifidobacterium dentium* (Barrett et al. 2012). Long-term administration of *L. rhamnosus* to rats modulates the expression of GABA in CNS, leading to reduced levels in the hippocampus, amygdala and locus coeruleus, but increased levels in cortical regions (Bravo et al. 2011). Furthermore, GABA decreases the levels of corticosterone induced by depression and anxiety-related symptoms (Mangiola et al. 2016). Mice treated with *Bifidobacterium longum* NC3001 revealed reduced anxiety-like behaviors (Bercik et al. 2010). The presented studies indicate that selected probiotics can be used successfully in treatment of depression and anxiety symptoms (Bravo et al. 2012).

Dietary factors can be associated with anxiety-like behaviors in mice, e.g. long-term high fat diet increased anxiety levels (Del Rosario et al. 2012). The mice fed with beef showed greater bacteria diversity and less anxiety-like behaviors in comparison to animals with standard chow diet (Li et al. 2009a).

A double-blind, placebo-controlled, randomized clinical trial with probiotic formulation (*L. helveticus* and *B. longum*) administered for 30 days alleviated psychological distress in healthy human volunteers (measured by the Hopkins Symptom Checklist) (Messaoudi et al. 2011). In a similar study, healthy female volunteers consumed fermented milk product with some probiotics for four weeks (*Bifidobacterium animalis subsp. Lactis, Streptococcus thermophilus, Lactobacillus bulgaricus* and *L. lactis subsp. Lactis*) indicated an influence on brain activity in emotion-related areas, e.g. reduced activity of sensory brain network, frontal, prefrontal and temporal cortices (Tillisch et al. 2013).

## Schizophrenia

Despite over 100-year history of research, the etiology of schizophrenia is still not fully understood, nonetheless, an interaction of environmental and genetic factors is still strongly considered (Joseph et al. 2017, Nemani et al. 2015). Schizophrenia typically develops at age between 15–45 years (Crow 1980) and has similar prevalence rates worldwide despite the different diagnostic criteria in various parts of the world (Arneth 2017, Sartorius et al. 1986). Due to the devastating course of untreated schizophrenia presenting with characteristic 'positive' (delusions and hallucinations) (Morris et al. 2013) and 'negative symptoms' (apathy, anhedonia, amotivation) (Rabinowitz et al. 2012) as well as dysfunctions in learning and memory (Gold et al. 1997), the patients

unquestionably require extensive care (Szkultecka-Debek et al. 2016).

Epidemiological studies showed that patients with schizophrenia, and members of their family, have a higher frequency of autoimmune disorders (Benros et al. 2012), atopic disease (Hornig 2013), and celiac disease (Dickerson et al. 2014). The latter is a risk factor for the development of schizophrenia (Severance et al. 2012) suggesting that schizophrenia is related to immuno-inflammatory activity (Karakula-Juchnowicz et al. 2016). The higher CRP serum levels in schizophrenic patients were found as a marker of inflammation (Dickerson et al. 2013), but the origin of inflammatory process is still unclear (Joseph et al. 2017). Polymorphisms in IL-1β, IL-6, and soluble IL-6 receptors (sIL6R) are postulated to be a risk factor for schizophrenia (Hudson and Miller 2016), and the correlation between inflammatory markers level and severity of clinical symptoms were recently reported (Hope et al. 2013).

Some authors indicate that immunological disturbances may result from a dysfunction of the brain-gut axis (Karakula-Juchnowicz et al. 2016) caused by LGS. Indicated evidence of damage to the intestinal barrier is: 1) histological (in 82 autopsies patients with schizophrenia were diagnosed with: colitis in 92%, enteritis in 88% and gastritis in 50% (Hemmings 2004, Karakula-Juchnowicz et al. 2016), 2) immunological – presence of intestinal inflammation markers (higher levels of food antigen antibodies: bovine milk casein and wheat-derived gluten (Severance et al. 2012), increased serum levels of proinflammatory cytokines, especially IL-1β, IL-6, IL-8 (Fillman et al. 2016, Miller et al. 2011), 3) by bacterial translocation markers, e.g., elevated serum levels of antibodies against *Saccharomyces cerevisiae* (Severance et al. 2012), serum elevation of bacterial markers, e.g. sCD14 and lipopolysaccharide binding protein- LBP (Severance et al. 2013). It was suggested that schizophrenia might also be associated with infection of *Clostridium difficile* producing phenylalanine derivative affecting CNS in a similar way as in autism (Shaw 2010).

Investigators have found that diet can change human behavior. It was shown that fermented foods improved cognitive function (Kim et al. 2016, Selhub et al. 2014). Moreover, schizophrenic patients present abnormal sensitivity to gluten and bovine casein (Cascella et al. 2011, Karlsson et al. 2012, Severance et al. 2010), and gluten free diet improved behavior and increased free L-tryptophan levels (Jackson et al. 2012) indicating that LGS can be responsible for gluten/casein sensitivity (Severance et al. 2012). Epidemiological studies show that metabolic syndrome is another clinical condition correlated with schizophrenia, its incidence is 20% higher than in general population (Mitchell et al. 2013). Ketogenic diet may improve the clinical course of schizophrenia, like normalization of behavior (probably by regulation of glutamate neurotransmission, GABA function and glucose metabolism), which supports the existing links between schizophrenia and GI tract (Kraeuter et al. 2015, Pacheco et al. 1965).

It is documented that gut microbiota affects the CNS by modulating: brain-derived neurotropic factor (BDNF), which expression is responsible for cognitive dysfunction (Nieto et al. 2013) and its decrease was found in patients with schizophrenia, anxiety disorders and Alzheimer's disease (Carlino et al. 2013, Sudo et al. 2004). BDNF expression is lower in GF animals correlating with increased anxiety behavior and progressive cognitive dysfunction (Carlino et al. 2013, Foster and McVey Neufeld 2013). The decreased level of NMDA in GF animals is responsible for controlling the synaptic plasticity in memory function in the cortex and hippocampus (Nemani et al. 2015, Sudo et al. 2004). NMDA receptor hypofunction is considered to be one of the most important pathophysiology of schizophrenia (Nemani et al. 2015). The gut microbiota modulates synaptophysin involved in the brain development (Douglas-Escobar et al. 2013, Nemani et al. 2015).

The current opinion suggests that gut dysbiosis may exert a harmful influence on brain development and functioning, regulation of immunology system and metabolic function in schizophrenia (Caso et al. 2016, Nemani et al. 2015), however, to date, there has been no direct evidence of dysbiosis in schizophrenia patients (Nemani et al. 2015).

Animal models are helpful to elucidate the role of gut microbiota in the pathogenesis of schizophrenia: it was shown that GF mice represent schizoid behavior (Caso et al. 2016). Furthermore, the behavioral deficits are more severe in males, similarly to human epidemiology of SCZ (Dinan et al. 2014). The social behavior in GF mice was examined by using classical 'three-chamber sociability test' showing that GF animals have problems in communication and with emotions recognition (Desbonnet et al. 2014).

Oral supplementation of mice by *Bacteroides fragilis* and resulting correction of gut permeability ameliorates defects in communication, anxiety-like and sensorimotor behaviours (Hsiao et al. 2013). Oppositely, treatment with *Lactobacillus rhammosus* and *Bifidobacterium animals subsp. Lactis* showed no significant effects on psychiatric symptoms (Dickerson et al. 2014).

In a 16-week clinical trial employing treatment with a second generation tetracycline- minocycline showed a reduction of negative symptoms in patients with early stage schizophrenia in SANS (Scale for the Assessment of Negative Symptoms), PANSS (Positive and Negative Syndrome Scale) and CGI (Clinical Global Impression Scale) (Liu et al. 2014).

Antibiotics and probiotics combined with a gluten and casein-free diet might have a therapeutic potential

in some schizophrenia patients (Latalova et al. 2017). To make dietary interventions successful support from scientists, dieticians, family members, and neuropsychiatric clinicians is necessary (Joseph et al. 2017). Further clinical trials are needed to confirm these theses.

## CONCLUSIONS

The prevalence of mental disorders is predicted to increase (Fond et al. 2015) and microbiologists, from Louis Pasteur and Ilya Mechnikov to the present, have tried to understand the role of microbiota for our health and in the pathogenesis of diseases (Backhed et al. 2005). Multiple studies, with antibiotic and probiotic treatments, fecal microbiota transplantation, and GF animal studies have been used to assess the impact of microbiota on brain function demonstrating differences between healthy human gut microflora composition and that of patients with neuropsychiatric diseases (Cryan and Dinan 2012, Dinan and Cryan 2013, Zhou and Foster 2015). It is well known that gut microbiota composition and functioning depends largely on diet, which consequently can affect also nervous system and metabolism, but these investigations need further studies (Moos et al. 2016). Identification of the signaling pathways between the microbiota and the brain in humans is needed to expand our understanding of microbiota gut–brain interactions. If confirmed, modulation of the gut microflora can be a novel target for the treatment (Tillisch et al. 2013).

Currently, most data examining brain-gut relationships have been collected in experimental animals, but they can be considered as valuable for future human studies (Principi and Esposito 2016). Although, it is not clear whether psychiatric diseases depend on gut microbiota modification or a single bacteria species (Principi and Esposito 2016), modification of gut microbiota and the gut-brain communication may be promising treatment for neuropsychiatric diseases.

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