

## ROLE OF GUT MICROBIOTA IN THE INTERACTION BETWEEN IMMUNITY AND PSYCHIATRY: A LITERATURE REVIEW

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### SUMMARY

**Background:** Psychiatric disorders may be correlated with a low-grade systemic inflammation but the origin of this inflammatory response remains unclear and both genetics and environmental factors seems to be concerned. Recent researches observed that gut microbiota seems to have an impact on the brain and immune processes.

**Method:** We review recent literature to a better understanding of how microbiota interacts with brain, immunity and psychiatric disorders. We search on Pubmed, PsycINFO, PsycARTICLES and Scencedirect articles with the keywords "gastrointestinal microbiota" and "mental disorders" or "psychological stress".

**Results:** We showed links between gut microbiota and brain-gut axis regulation, immune and endocrine system activity, neurophysiological changes, behavior variations and neuropsychiatric disorders. Communications between brain and gut are bidirectional via neural, endocrine and immune pathway. Microbiota dysbiosis and increase gut permeability with subsequent immune challenges seems to be the source of the chronic mild inflammation associated with neuropsychiatric disorders. Repeated immune or stress events early in life may lead to neurodevelopmental disorders or sickness behavior later in life.

**Conclusions:** psychological stress impact gut microbiota with subsequent immune activation leading to neurodevelopmental disorders or sickness behavior and altering neurophysiology and reactivity to stress or lifestyle.

**Key words:** microbiota - psychological stress - psychiatric disorder - immunity

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### INTRODUCTION

We highlighted in a precedent review (Dubois et al. 2018) that psychiatric disorders may be correlated with a low grade systemic inflammation and mild immunosuppression. The origin of this inflammatory response remains unclear and both genetics and environmental factors seems to be concerned. Recent researches observed that gut microbiota seems to have an impact on the brain and immune processes. In this article we review recent literature to a better understanding of how microbiota interacts with brain, immunity and psychiatric disorders.

### METHOD AND LIMITATIONS

We search on Pubmed, PsycINFO, PsycARTICLES and Scencedirect articles with the keywords «gastrointestinal microbiota» and «mental disorders» or «psychological stress». We have as much as possible promoted recent literature (2012 to early 2019) and human studies but they are limited and sometimes have a lower statistical significance than animals studies. We have been focused on the literature about immunity and endocrine system. Selection and interpretation bias are probably present for the subsequent conclusions.

### RESULTS

#### Links between intestinal microbiota and brain-gut axis

We found several evidences emphasizing the fact that brain – gut axis is influenced by micro-organisms colonising the gut mucosa (gut microbiota). Enteric

nervous system (ENS) and central nervous system (CNS) are connected through the vagus nerve. Evidences showed that gut microbiota directly in contact with the ENS could modulate sensory neurons excitability and so information relayed to the brain (Parashar & Udayabanu 2016). Neurotransmitters such as catecholamines or gamma-aminobutyric acid (GABA) (Asano et al. 2012, Barret et al. 2012) are secreted by intestinal microbiota. Bacteria metabolism influences the serotonergic system by altering tryptophan availability to 5-HT synthesis (Rackers et al. 2018). There is evidences that host neurophysiology is modulated by changes in gut microbiota. Neufeld et al. (2011) observed changes in hippocampal brain derived neurotrophic factor (BDNF) mRNA in germ-free (GF) mice.

#### Links between intestinal microbiota and behavior

Significant evidences support correlations between behavior and gut microbiota composition. It was showed that intestinal microbiota influences sensitivity to stress. Huo et al. (2017) showed less anxiety-like behavior in GF mice while others studies showed opposite results (Crumevolle-Arias et al. 2014). Desbonnet et al. (2014) found a significant social behavior impairment in GF mice. These behavior shifts were normalized following colonization of the gut of GF mice. Short-chain fatty acids (SCFA) such as butyrate, acetate or propionate (PPA) are produced by microbial fermentation of dietary fiber and is a common preservative added to refined wheat and dairy products. SCFA are known to have neuroactive properties or induce neuroinflam-

mation and are associated with behavioral alterations. It was showed that PPA activate microglia of the hippocampus, white matter, cingulate, and neocortex (MacFabe et al. 2011) and can also alter the excitatory and inhibitory balance in neural circuitry via increased glutamatergic and decreased GABAergic transmission (MacFabe 2012). PPA seems to be linked with autism spectrum disorder symptomatology in human. Higher autistic symptoms are observed after eating food containing PPA and improvement is observed following the elimination of these product (Cenit et al. 2017).

### **Links between intestinal microbiota and immune system**

Moreover, it seems that endocrine and immune system play an important role in the interaction between microbiota and brain. Microbiota composition may interact with hypothalamic-pituitary-adrenal (HPA) axis activity. Huo et al. showed a greater increase of HPA axis hormones levels with increased corticotrophin releasing factor (CRF) expression, elevated adrenocorticotropic hormone (ACTH) with corticosterone/cortisol levels and a reduce glucocorticoid receptor (GR) expression in GF stressed mice (Huo et al. 2017). Furthermore, stress may affect the composition of the gut microbiota and increase gut permeability (Kelly et al. 2015). Catecholamines are known to induce growth of gram negative bacteria (Lyte & Ernst 1992). CRF might play a role in the stress-induced gut permeability dysfunction (Rodiño-Janeiro et al. 2015). Vanuystel et al. (2014) showed in humans that the mechanism might be the activation of mast cells receptors for corticotropin-releasing hormone. An increase gut permeability or a «leaky» gut facilitates translocation of bacteria into intestinal wall and contribute to the development of local inflammation but also the inflow of bacterial metabolites or harmful substance. Leading to a chronic systemic low-grade inflammation characterized by an increase level of pro-inflammatory cytokines and an activation of the HPA axis and secretion of cortisol (Brzozowski et al. 2016). Lipopolysaccharide (LPS) is a constituent of the outer membrane of Gram-negative bacteria. Toll-like receptor (TLR) are pattern recognition receptors (PRR) expressed by macrophages. LPS binds to TLR4 leading to nuclear factor-kB (NF-kB) activation and pro-inflammatory cytokines upregulation and so activation of immune system in the periphery and brain as well as stimulate the HPA axis (Mayerhofer et al. 2017). Moreover lipopolysaccharide (LPS) is known to produce systemic and psychiatric changes called sickness behavior such as fatigue, anorexia, depressed mood or apathy (DellaGioia & Hannestad 2010).

### **Links between intestinal microbiota and early life psychological stress**

On Wah et al. (2018) showed in rats that early life immune challenges (induce by repeated LPS administration during adolescence or early adulthood) may induce

effects long after initial response has dissipated and are risk factor for neurodevelopmental disorders or sickness behavior later in life (such as anxiety or depressive-like behavior). Moreover, they demonstrated that administration of PPA later in life may potentiate symptoms and sickness behavior due to the priming effect of LPS. Perinatal period, early childhood and adolescence are reported to be vulnerable periods for both brain and gut microbiota development. Animals studies showed that stressful events and subsequent gut-brain axis dysregulation early in life lead to brain development perturbations and have consequences on behavior such as anxious-like or social behavior or cognitive function and even immune or metabolic disorders in adulthood (Stiemsma & Michels 2018, Desbonnet et al. 2015). Dysregulation of gut-brain axis early in life is correlated with dysbiosis, reduce BDNF, HPA axis activation, impaired GR-mediated negative feedback and increase stress reactivity in adulthood (Desbonnet et al. 2015, Malan-Muller et al. 2018, Farzi et al. 2018). Moya-Pérez et al. (2017) showed that *Bifidobacterium* (*B. pseudocatenulatum* CECT 7765) intake may modulate the consequences of chronic stress on the HPA axis in adulthood with positive consequences in brain biochemistry and behavior.

### **Links between intestinal microbiota and neuropsychiatric disorders**

Evidences revealed that a disturbance of the intestinal ecosystem (dysbiotic microbiota) might be associated with gastro-intestinal disorders but also with neuropsychiatric disorders (Gulas et al. 2018). Functional gastro-intestinal disorders such as inflammatory bowel disease (IBD) or irritable bowel syndrome (IBS) are characterized by a stress-induced brain-gut-microbiota alterations and are often associate with psychological distress including anxiety or depression (O'Mahony et al. 2017). But also it was observed that gastrointestinal (GI) symptoms are common in individuals with autistic spectrum disorder (ASD) and studies suggested a microbiota imbalance and an increase gut permeability (or «leaky gut»). It is demonstrated that ASD is correlated with an increase inflammatory markers (such as IL-6 or TNF), immune cells infiltration in the GI tract and increased levels of IgA in stool sample. A recent study performed fecal transplantation in ASD and observed a significant improvement in both GI and behavioral ASD symptoms (Groen et al. 2018, Fowlie et al. 2018). Depressive disorder is correlated with shifts in the microbiome composition (Zhernakova et al. 2016). Variations in levels of Bacteroidetes, Proteobacteria, Actinobacteria and Firmicutes are observed in depressive patients stools compared to controls. But studies showed contradictory results concerning proportions of species represented in stools samples (Jiang et al. 2015, Zheng et al. Lin et al. 2017). Consumption of *Lactobacillus* and *Bifidobacterium* is related with a small but significant improvement of depression score in a double-blind

randomized placebo controlled study (Messaoudi et al. 2011). When transferring microbiota from patients with major depression to microbiota-depleted animals characteristics of depression are also transferred (Cenit et al. 2017). In recent findings it was showed that human gut microbiota is involved in host metabolism and weight regulation. Dysbiosis is also demonstrated in anorexia nervosa (AN). Studies found an increase concentration of *Methanobrevibacter Smithii* (*M. Smithii*) in patients with AN compared to individuals with normal weight or obese controls. Moreover, negative correlation are found between body mass index and increased concentration of *M. Smithii* (Seitz et al. 2019).

## DISCUSSIONS

### Microbiota dysbiosis is associated to behavior alterations and neuropsychiatric disorders

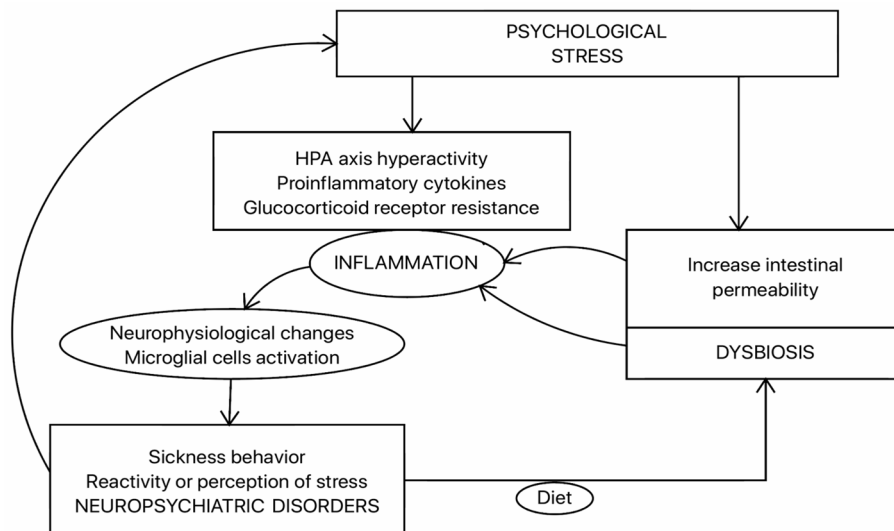
The human gut microbiota includes more than 1,000 species and over 7,000 subspecies. Bacteroidetes (composed by several bacteroides or prevotella species) and Firmicutes (such as *Clostridium*, *Ruminococcus*, *Lactobacillus*) are the most abundant phyla in the gut. Actinobacteria (such as *bifidobacterium*), Proteobacteria (*Enterobacteriaceae* such as *Escherichia coli*), Verrucomicrobia, Fusobacteria, Cyanobacteria and Spirochaetes are also found in intestinal flora. In adults, the intestinal microbiota consists of strictly anaerobic bacteria and relatively anaerobic bacteria are found but only in small amounts. Composition of microbiota is not constant during lifetime. The development occurs during early childhood and depends for example on maternal health or mode of delivery. After the age of three years the gut microbiota is relatively stable and tends to lose diversity in the elderly (Gulas et al. 2018). We showed that dysbiotic microbiota is connected with gastrointestinal disorders such as inflammatory bowel disease or irritable bowel disease but also with neuropsychiatric disorders such as depression, anxiety, autism or anorexia. Animals model is the most representative to understand the impact of intestinal dysbiosis on the brain and behavior. A total absence of microorganism is characterized by GF mice model correlated with behavior alterations such as impairment in social behavior, anxiety-like behavior and more reactivity to stress. There is also neuro-endocrine changes such as HPA axis hyperactivity and reduce GR expression but also neurophysiological perturbations such as a decrease of BDNF levels in hippocampal region. Dysbiosis is related to change in bacteria constituent or metabolites. Some species seems to have harmful and other protective effects but it is difficult actually to associate specific pattern of dysbiosis with a behavior or a psychiatric disorder. Administration of probiotics or improvement in lifestyle and diet in depressive patients or ASD are correlated with improvement of the symptomatology. Recently fecal microbiota transplant showed that the phenotype of the donor is transferred to the recipient.

### There is bidirectional communications between gut and brain

Interactions between the gastrointestinal tract and the cerebral nervous system (CNS) are more commonly called «brain-gut axis». Within the digestive tract we found millions of neurons forming the ENS whose the role is to regulate autonomic function of the gut such as motricity or secretions. ENS is connected to the brain via vagus nerves. It is well known that emotions such as stress may be accompanied by transit perturbations. Furthermore, we showed that commensal microorganism living along the gut have also the possibility to interfere with autonomic nervous system. Bacteria may secrete several neurotransmitters implicated in communication within the ENS and also CNS. Besides microbiota dysbiosis it is especially through the disturbance of gut permeability that a gut-brain axis dysregulation may be observed. In fact an increase gut permeability (called «leaky» gut) is associated with more bacterial constituents (LPS) or metabolites passing by the blood inflow to the brain or infiltrating the gut mucosa. The mechanisms by which psychological stress result in a «leaky» gut seems to be multiple and probably involve vagus nerve and ENS but also neuroendocrine and immune system with a direct activation of mast cells receptors with corticotropin-releasing hormone (CRF). The subsequent effect of macrophages activation via LPS/TLR interaction is upregulation of pro-inflammatory cytokines and local and/or chronic systemic low-grade inflammation.

### Gut microbiota as the source of inflammation leading to psychiatric disorders

Psychological and gastro-intestinal symptoms are often associated in inflammatory bowel disorders but also in psychiatric disorders. This is particularly demonstrated in ASD given both local inflammation and systemic low-grade inflammatory marked by pro-inflammatory cytokines. In a precedent review (Dubois et al. 2018) we showed that a similar chronic mild inflammatory response seems to be involved in most of psychiatric disorders. Cytokines may cross the brain blood barrier (BBB) and activate microglial cells to express more cytokines in the brain. Cytokines may activate indoleamine 2,3-dioxygenase (IDO) transforming tryptophan into kynurenine instead of serotonin. Some bacteria in the gut are also involved in tryptophan metabolism altering tryptophan availability to 5-HT synthesis. Subsequent kynurenine metabolites may interfere with glutamatergic pathway and induce oxidative damage to limbic structures or cognitive impairment. Oxidative stress leads to a reduction of brain derived neurotrophic factor (BDNF) and an activation of nuclear factor kB (NFkB) leading to an upregulation of pro-inflammatory cytokines. These brain alterations are similar to what is observed in some microbiota studies. Particularly studies concerning short-chain fatty acids (SCFA) such as propionate (PPA) having the capacity to activate microglia and alter glutamatergic/GABAergic balance in neural circuitry and induce neuroinflammation.



**Figure 1.** Hypothetical model of interactions between psychological stress, inflammation and gut microbiota

## CONCLUSION

We showed that interactions between gut microbiota, psychological stress, psychiatric disorder and immunity are well documented but not fully understood. Acute stress activate HPA axis and pro-inflammatory cytokines and as hypothesized psychological stress have also an impact on gut microbiota and may lead to a deficiency of the intestinal barrier with subsequent immune system activation. Dysbiosis seems to play an important role in this immune challenge. Psychological distress may impact bacteria composition and ecosystem of gut microbiota. It seems that variations in composition is related to change in bacteria constituent or metabolites. Some species seems to have harmful and other protective effects (Figure 1).

Psychological stress and so repeated immune challenges during more vulnerable period for the brain such as perinatal period, early childhood or adolescence may lead to neurodevelopmental disorders or sickness behavior later in life. Early life inflammation may affect neurophysiology and microglial cells development and activity and psychological stress later in life lead to an exacerbated inflammatory response. Psychiatric disorders are often correlated to a chronic systemic low grade inflammation with concomitant mild immunosuppression. Sickness behavior and eventually psychiatric or neurodevelopmental disorders altering reactivity or perception of stress events and are also associated with poor lifestyle or unhealthy diet directly impacting gut microbiota.

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### Contribution of individual authors:

Thomas Dubois, Christine Reynaert, Denis Jacques, Lepiece Brice & Nicolas Zdanowicz all made substantial contributions to conception and design and or acquisition of data and/or analysis and/or interpretation of data.

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