

Mental Health

AND GUT MICROBIOTA

Towards new therapeutic avenues?

BIOCODEX 
Microbiota Institute

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1. GUT-BRAIN AXIS: A COMMUNICATION PATHWAY TO BE EXPLORED



Our gut, often called our “second brain”, owns **200 million neurons (enteric nervous system)**, hosts **several billion gut bacteria** and tract is constantly sending information to our brain, and conversely. **But this bidirectional communication can be disrupted when our gut microbiota is impaired and an inflammatory process takes hold. An impairment of the gut-brain axis could be involved in the onset of neuropsychiatric disorders¹.**



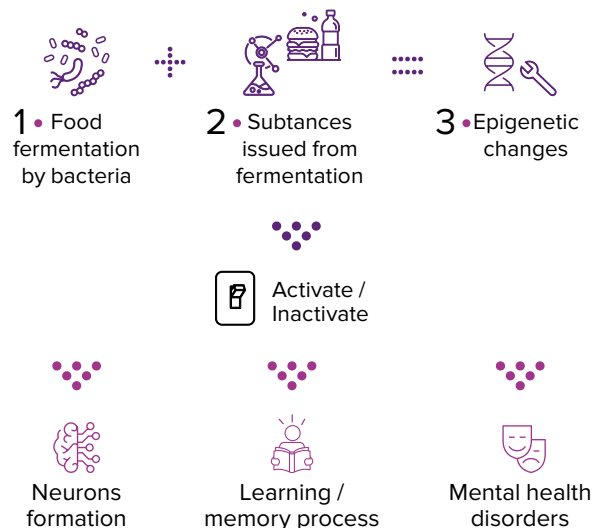
When the microbiota plays with our genes

Formation of new neurons, learning or memory process, as well as mental health disorders (schizophrenia, depression...) could be associated with “epigenetic” changes. The latter impact the expression of some genes* (activating or, on the contrary, deactivating them), but in a reversible way.

As gut bacteria could be the source of epigenetic changes, especially through fermentation products of dietary fibers, scientists are trying to determine whether the microbiota could be involved in the development of some neuropsychiatric disorders through these genome disruptions[†].

*elements located on DNA-containing chromosomes and responsible for the transmission of hereditary traits (eye color...)

†genetic material of an organism (most often DNA)



¹ Cenit MC et al. *Influence of gut microbiota on neuropsychiatric disorders*. World J Gastroenterol. 2017

1 • GUT-BRAIN AXIS: A COMMUNICATION PATHWAY TO BE EXPLORED

Research on the gut-brain axis is gradually revealing the processes used by gut bacteria to communicate with the brain. We now know that exchanges between brain and gut are based on 4 main pathways: neural, hormonal, immune, and metabolic.

The two “organs” communicate through the vagus nerve which goes from the skull to the abdomen and plays a role in several vital functions such as heart rate. Patients who underwent a vagus nerve ablation are incidentally less likely to develop neurological disorders.

Gut-brain axis²: what is it?

Gut bacteria communicate with the brain by producing chemical molecules called “neurotransmitters” (serotonin, dopamine, GABA³...). These microbial molecules do not act directly on the brain, which is isolated and protected by a membrane called the blood-brain barrier. It appears that neurotransmitters produced by gut bacteria act on the cells lining the gastrointestinal wall in order to have them transmit their message to the central nervous system through the neurons of the gastrointestinal tract that are connected to the brain. Short chain fatty acids (SCFA) are biological sub-

stances, some of which have a beneficial and protective effect, produced by colon bacteria during the fermentation process of dietary fiber⁴. They play an important role in the communication between the two organs by acting directly on the brain.

Alternative routes

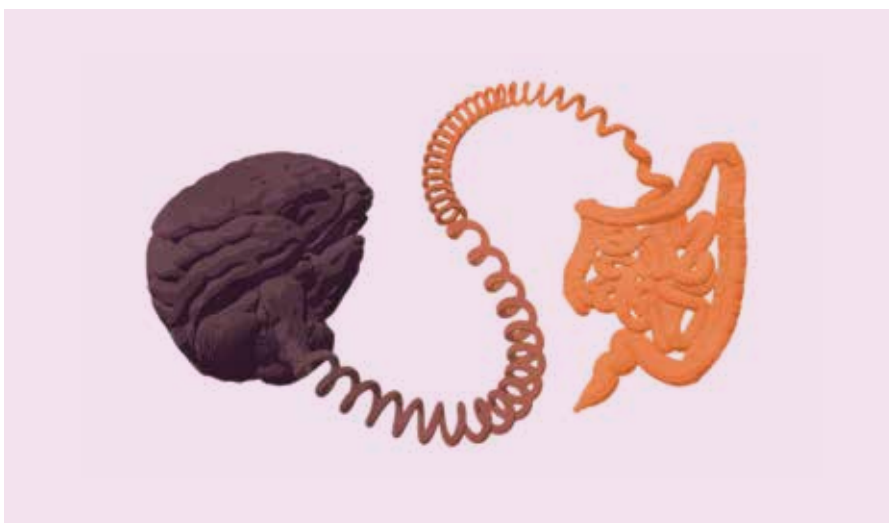
Other possible pathways are the immune system and the blood flow. Thanks to SCFA, gut bacteria can stimulate some white cells, which are responsible for defending our organism. Those white cells then produce chemical messengers (cytokines) that can cross the intestinal wall, move into the bloodstream, and cross the blood-brain barrier. They then act on the brain, mainly on regions involved in the regulation of stress response. The brain acts on the intestines by modulating secretions, motility and blood flow, and as such, it affects gut permeability⁵.

Is there a link between microbiota and brain functions?

All studies conducted on animals show that gut bacteria impact brain development, throughout life: creation of new neurons in the brain, development of new neural connections⁶, involvement in the transmission rate of electrical



signals delivered by neurons, memory, social behavior, regulation of stress hormone (cortisol)... Without bacteria, our brain would be distressed and more vulnerable to infectious agents or toxic molecules⁷.



² Skonieczna-Zydecka K, et al. Microbiome-The Missing Link in the Gut-Brain Axis: Focus on Its Role in Gastrointestinal and Mental Health. J Clin Med. 2018 Dec 7

³ Gamma-aminobutyric acid, responsible for controlling fear and anxiety, among others

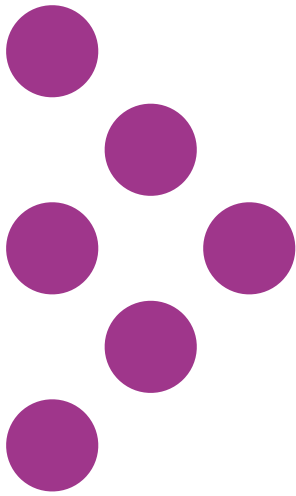
⁴ Mainly acetate, butyrate and propionate

⁵ Dinan TG, et al. The Microbiome-Gut-Brain Axis in Health and Disease. Gastroenterol Clin North Am. 2017 Mar

⁶ Cenit MC et al. Influence of gut microbiota on neuropsychiatric disorders. World J Gastroenterol. 2017

⁷ Sharon G et al. The Central Nervous System and the Gut Microbiome. Cell. 2016 Nov 3

2 • WHAT ABOUT DEVELOPMENTAL DISORDERS?⁸



Microbiota disruptions in the first years of life, when our intestinal flora and brain are developing, can affect brain structures and functions and promote developmental disorders. Autism spectrum disorders (ASD) include a number of contrasted disorders associated to brain development defects. They could be related to a microbiota disruption induced by pregnancy and during the first few years of life: some gastrointestinal signs, frequently associated to this disorder, led scientists to believe that the microbiota was undoubtedly a way of understanding autism spectrum disorders.

Symptoms appear early in life and include communication deficit, social communication and behavior disorders as well as repetitive behaviors. Compared to the general population, affected people are more subject to gastrointestinal disorders (diarrhea, abdominal pain, constipation), whose severity seems sometimes related to that of the disease's symptoms.

Microbial “signatures”?

Autistic children seem to have a less diversified flora than healthy children: it has lower contents of bacteria known to be beneficial such as *Bifidobacterium*, and higher contents of others (*Lactobacillus*, *Clostridium*...). Moreover, autistic children intestines seem to host more *Candida* (especially *Candida albicans*) than usual. But

this fungus produces ammoniac and toxins that can impact the brain's functioning and exacerbate intestinal bacterial disorders.

Several risk factors

In animals, a high-fat maternal diet during pregnancy could be associated to an imbalance of the gut microbiota—called “dysbiosis”—and the onset



OPEN WIDE AND SAY “AH”: THE NEW DIAGNOSTIC TEST FOR AUTISM⁹

❖ Current screening is based on behavioral, psychomotor, psychological and language signs. It is possible to establish a diagnosis as early as the age of 2, but diagnostic delay is frequent.

❖ A recently developed 96%-accurate mathematical algorithm seems to be very promising and could be added to the diagnostic arsenal: it was tested on 32 affected children and could help detect new autism biomarkers (exceeding amounts of “bad” bacteria and decreased diversity) in the oral flora (saliva and dental plaque).

⁸Li Q et al. *The Gut Microbiota and Autism Spectrum Disorders*. Front Cell Neurosci. 2017 Apr 28. doi:10.3389/fncel.2017.00120

⁹Qiao Y, Wu M, Feng Y, Zhou Z, Chen L, Chen F. *Alterations of oral microbiota distinguish children with autism spectrum disorders from healthy controls*. Scientific Reports, 2018. 10.1038/s41598-018-19982-y

2• WHAT ABOUT DEVELOPMENTAL DISORDERS?

of autistic disorders in their offspring. Children born through C-section who received many antibiotics also seem to have a higher risk of developing these disorders. The upside is that breast-feeding during the first 6 months of life (minimum) could decrease the risk of developing these disorders at a later age.

Microbiota: a therapeutic hope?

A few avenues are under investigation: probiotics for instance, which could improve gastrointestinal disorders and relieve autistic symptoms, similarly to some antibiotics. Despite a significant infectious risk, fecal transplant¹⁰ could also be useful to reduce autistic behaviors and associated gastrointestinal disorders⁷ in children and adolescents. Finally, diet is of great interest. The use of omega-3 supplements could improve behavior: a diet free of gluten or milk proteins as well as a high-fat low-carb diet (called “ketogenic”) could increase sociability as well as the ability to communicate and decrease stereotyped behaviors.



¹⁰ Fecal transplant from healthy donor(s) aimed at restoring the balance of microorganisms in the recipient patient

Attention deficit disorders* WITH OR WITHOUT HYPERACTIVITY^{11 12 13}



Attention deficit disorders, with or without hyperactivity, can affect people of all ages. It is estimated that 5% of children in the world are affected.



People with attention deficit disorders have a lot of trouble concentrating, they are impulsive and agitated.



Besides genetics, environment is a significant risk factor (stress during pregnancy, delivery mode, diet...).



Diet rich in fish, low in sugar and with no additives or artificial coloring and flavors during childhood seems to improve symptoms and even reduce the risk of developing the disease in adolescence.

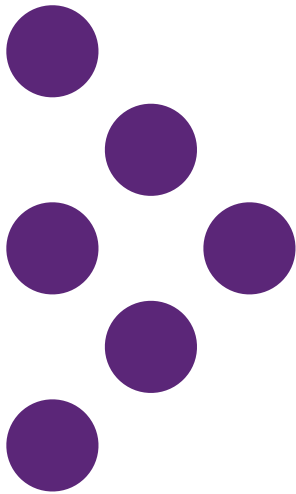
* ADHD

¹¹ Cenit MC, Nuevo IC, Codoñer-Franch P. *et al.* Eur Child Adolesc Psychiatry (2017) 26: 1081. doi.org/10.1007/s00787-017-0969-z

¹² Cenit MC, *et al.* Gut microbiota and attention deficit hyperactivity disorder: new perspectives for a challenging condition. Eur Child Adolesc Psychiatry. 2017 Sep. doi.org/10.1007/s00787-017-0969-z

¹³ Lange K. *Current Opinion in Clinical Nutrition and Metabolic Care.* (2017). doi: 10.1097/MCO.0000000000000415

3. ANXIETY DISORDERS ARE NOT THE EXCEPTION



They affect more than one person out of five (aged 18 to 65 years) at least once in their lifetime¹⁴. Family history increases vulnerability to ADHD, but people who are not predisposed are not immune. Chronic anxiety is at least partially associated to inflammatory processes that are potentially promoted by gut bacteria. Constant and excessive worry difficult to control, unpredictable and regular panic attacks, obsessive-compulsive disorders, post-traumatic stress disorder... Anxiety disorders refer to various diseases whose common thread is fear. These patients are prisoners of their fears and implement disproportionate avoidance strategies.



Among other factors is, once again, gut dysbiosis! It leads to an increase of intestinal permeability and a disruption of stress response, as well as an increase in inflammatory activity.

All roads lead to the microbiota¹⁵

Scientists agree that gut bacteria play a role in this process. But according to scientific studies, the microbiota could either have an anxiety-inducing effect or an anxiolytic effect¹⁶. The use of antibiotics—that disrupt and impoverish the gastrointestinal flora—could be associated to the onset of anxiety disorders, or conversely, to a decrease in anxiety in animals.

The flora is being explored “blindly”

In animal models, antibiotics seem to decrease anxiety during the treatment period. The drawback is that an early disruption of the gut microbiota by antibiotics could lead to behavioral changes that persist into adulthood^{17,18}. Some probiotic strains could also have an anxiolytic effect. Finally, fecal microbiota transplant could reduce anxiety levels¹⁹. All these results still have to be confirmed in humans.

What to eat to stay zen?

Fermented foods such as cheese, yogurts, kefir, kombucha or soy sauce

are excellent sources of probiotics and prebiotics. They act as anti-inflammatory agents by strengthening the

¹⁴ www.anxiete.fr

¹⁵ Aslam H et al. *Fermented foods, the gut and mental health: a mechanistic overview with implications for depression and anxiety*. Nutr Neurosci

¹⁶ <https://dumas.ccsd.cnrs.fr/dumas-01845349/document>

¹⁷ Leclercq S, Mian FM, Stanis AM et al. *Low-dose penicillin in early life induces longterm changes in murine gut microbiota, brain cytokines and behavior*. Nat Commun 2017; 8 : 15062 doi : 10.1038/ncomms15062

¹⁸ Tochitani S, Ikeno T, Ito T et al. *Administration of non-absorbable antibiotics to pregnant mice to perturb the maternal gut microbiota is associated with alterations in offspring behaviour*. PLoS One. 2016 Jan 20;11(1):e0138293. doi: 10.1371/journal.pone.0138293

¹⁹ Bercik P et al. *The intestinal microbiota affects central levels of brain-derived neurotrophic factor and behavior in mice*. Gastroenterology 2011; 141 : 599-609

3• ANXIETY DISORDERS ARE NOT THE EXCEPTION



Healing

BODY AND MIND²⁰

Psychobiotics are live microorganisms (bacteria, for instance) which, once ingested, produce a beneficial effect on the health of patients with psychiatric, psychological or neurological disorders.

In brief, they are probiotics that could have psychotropic properties and regulate the gut-brain axis by:



❖ Producing chemical messengers responsible for delivering information to the brain



❖ Directly activating neural pathways between brain and intestines



❖ Improving the balance between energy intake and expenditure



❖ Limiting increase of pathogenic bacteria in the stomach and intestines



❖ Limiting inflammatory processes in the gastrointestinal tract



❖ Protecting the intestinal barrier

integrity of the intestinal barrier, improving the composition and function of gut bacteria, and stimulating immune cells in the digestive tract. Probiotics decrease frequency and severity of anxiety symptoms in rat mod-

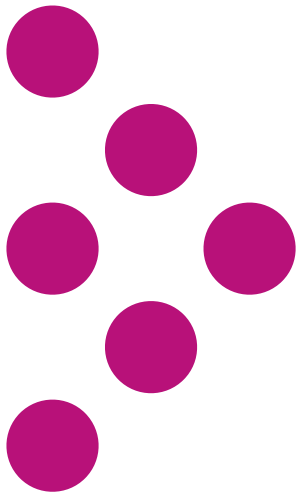
els. In humans, they decrease cortisol levels in urine²¹. In healthy people with no psychiatric disorders, consumption of fermented milk leads to changes in brain activity in regions that are responsible for emotions and pain.

20 Misra S, Mohanty D. *Psychobiotics: A new approach for treating mental illness?* Critical Reviews in Food Science and Nutrition, DOI: 10.1080/10408398.2017.1399860. 2017

21 Aslam H et al. *Fermented foods, the gut and mental health: a mechanistic overview with implications for depression and anxiety.* Nutr Neurosci



4 • MOOD DISORDERS



Depression and bipolarity are serious mental health disorders that are relatively common and sometimes associated to suicidal thoughts. The former affects more than one person out of five at least once in their lifetime. The latter, difficult to diagnose, affects 1 to 2.5% of people. Both diseases could be related to a gut dysbiosis which is sometimes correlated to the severity of the symptoms.

Depression

It manifests itself by unusual sadness, loss of interest, inability to perform daily tasks, greater fatigue and is accompanied by an increase of cortisol levels²², and thus a disruption of stress response.

In animals, the absence of gut microbiota (or its disruption) is associated to depressive symptoms and to an imbalance of neurotransmitters (serotonin, dopamine, GABA...). Furthermore, inflammation-inducing molecules that are present in excess in the blood and produced by gut bacteria, seem directly related to the development of depression²³. Although there are few, studies made in humans seem to have brought to light a bacterial signature: very recently, researchers discovered for instance that low levels of some bacterial genera in the intestines (*Coprococcus* and *Faecalibacterium*) are related to a feeling of poor quality of life in depressed patients.

Balanced gut, balanced mind

The administration of some probiotics, such as *Lactobacillus* and *Bifidobacteria* (bacteria from the Firmicutes phylum that are present at low levels in affected people) could be beneficial and be used as a supplement to antidepressant and anxiolytic



tic treatments currently used. Initial results are encouraging: prolonged use can relieve depressive symptoms and psychological distress, without causing adverse events²⁴.

Change your shopping list

It would seem that high-glucose transformed products could increase predisposition to depression. In depressed patients, prebiotics (mainly galacto-oligosaccharides found in red beans, chickpeas, artichokes...) could act positively by stimulating the increase of bifidobacteria²⁵. Opting for fruits, vegetables, fish (rich in omega-3 fatty acids) could restore the microbiota, regulate pro-inflammatory processes, and thus favorably impact

mood. Turmeric could decrease cortisol levels in the saliva and increase gut flora diversity, resulting in positive effects on the state of mind and behavior.

22 <http://www.euro.who.int/fr/health-topics/noncommunicable-diseases/mental-health/news/news/2012/10/depression-in-europe/depression-definition>

23 Hayley S, Audet MC, Anisman H. *Inflammation and the microbiome: implications for depressive disorders*. Current Opinion in Pharmacology, 2016, <https://doi.org/10.1016/j.coph.2016.06.001>

24 Vlajnić JV, Šuran J, Vlajnić T, Vukorep AL. *Probiotics as an Adjuvant Therapy in Major Depressive Disorder*. Curr Neuropsychopharmacol. 2016;14(8):952-958

25 Dinan TG, et al. *Feeding melancholic microbes: MyNewGut recommendations on diet and mood*. Clin Nutr. 2018 Nov 17

Bipolar disorders

They are characterized by swings between phases of depression and phases of overexcitement called “manic episodes”. The composition of patients’ gut microbiota is different from that of healthy individuals and its diversity is particularly reduced in affected women.

Bipolar patients (as well as schizophrenics) have increased levels of antibodies against fungi (*Saccharomyces cerevisiae* and *Candida albicans*) that are naturally present in the gastrointestinal tract. The presence of a specific protein in the blood indicates that bacteria usually located in the intestines were able to migrate. Moreover, concentrations of anti-*Saccharomyces cerevisiae* antibodies are higher in treatment-naïve patients than in those who are treated

with antipsychotics. These observations strengthen the hypothesis of a link between disease and inflammation²⁶.

Is nutrition education an avenue to pursue?

Yes, without a doubt, according to some psychiatrists who rely on diet to reduce inflammation and restore gut microbiota balance²⁷. Actually, a link between Western diet (high intake of carbohydrates and fat) and a disruption of neural and inflammation activity has been demonstrated. On the contrary, Mediterranean diet is the example to follow: it could have a protective effect against bipolar disorders as well as depression. The same could be said of omega-3 intake.

26 Nguyen TT, Kosciulek T, Eyler LT, Knight R, Jeste DV. Overview and systematic review of studies of microbiome in schizophrenia and bipolar disorder. *Journal of Psychiatric Research*, 2018

27 Beyer JL, Payne ME. *Nutrition and Bipolar Depression*. Psychiatric Clinics of North America, 2016



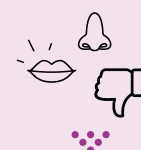
Schizophrenia



First described over a century ago, schizophrenia is one of the more complex and more mysterious psychiatric diseases. Patients are subject to hallucinations, they have trouble concentrating, memory impairment, and confused thinking.



The gut flora of patients who suffered their first psychotic episode is altered compared to healthy people and microbiota composition seems to be associated to the severity of symptoms.



The more the microbiota of schizophrenic patients is altered, the less likely they are to see their health status improve after one year. Oropharyngeal (mouth, nose, throat) microbiota in schizophrenic patients is less diversified and has a different composition from the general population.



Professor Emmanuel Haffen is a psychiatrist at the Besançon Teaching Hospital and director of the Laboratory of Integrative and Clinical Neuroscience in Besançon (France). He specializes in mood disorders and studies the links between depression, inflammation and gut microbiota. He explains why taking into consideration the intestinal flora can lead us to rethink psychiatric care.

Why is the psychiatric field interested in the microbiota?

This interest is relatively new. It stems from studies published less than 10 years ago showing that some stress factors have an impact on the digestive barrier, making it more permeable, thus allowing gut bacteria to cross into the bloodstream. This phenomenon leads to the production of inflammatory molecules at the intestinal level, that would then travel to the brain and disrupt it. This inflammation impairs the synthesis of serotonin, a chemical messenger produced in the intestines

and the central nervous system and involved in depression. Instead of producing serotonin, the body produces a toxic substance which destroys neurons and neural connections. We believe that the gut microbiota imbalance could trigger this cascade of events.

What is the link between microbiota and mood disorders?

Depressed individuals have an overrepresentation of some bacterial families, the presence of bacteria that are not found in healthy people, as well as bacterial species associated to an increase in the severity of the depressive episode. We also know that some gut bacteria synthesize dopamine and serotonin, two molecules responsible for regulating mood, among others. An

From depression to addiction, is there only one step?

The link between gut microbiota and addiction should be studied. Nowadays, the research focus is mainly on alcohol dependency, which is known to alter the digestive barrier. A few years ago, in Belgium, scientists demonstrated that there is a correlation between alcohol consumption, dependency and microbiota: dependent patients who have a strong disruption of the digestive barrier are those who present the most severe anxiety and depression disorders and the strongest desire to drink. They are also the patients who are most at risk to relapse. Their intestinal flora is different from that of patients who are at low risk of relaps-

“ **SCIENTISTS DEMONSTRATED THAT THERE IS A CORRELATION BETWEEN ALCOHOL CONSUMPTION, DEPENDENCY AND MICROBIOTA** ”

imbalance of these bacteria would thus have an impact on the functioning of the brain. The disruption of the gut microbiota could thus be related to the onset of a depressive illness and/or symptom severity. This is why, my team and I are about to study the interest of the use of probiotics in depressed patients: we want to see if we can improve depression symptoms by modulating the microbiota.

ing. French researchers have shown that apple pectin (a type of carbohydrate mainly found in the skin and seeds of apples) restores the digestive barrier in alcohol dependent rodents. This promising study is the first to demonstrate that diet can be a protective factor against addiction, although results are not yet applicable to humans.



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