

**GUT MICROBIOTA**  
RESEARCH & PRACTICE  
edited by ESNM

# GUT MICROBIOTA & GUT-BRAIN AXIS

A selection of content from the  
Gut Microbiota for Health 2016

January 2017

# SUMMARY

The digestive tract and the brain are intimately linked - this, scientists have known for many years. What's newer is the idea that the microbial communities living in the gut have a major role to play in how the gut and the brain communicate. Emerging scientific insights about the gut-brain axis are of particular interest in neurogastroenterology, the subspecialty of gastroenterology focusing on connections between the central nervous system and the enteric nervous system. As an organization dedicated to sharing new research in this particular field, the ESNM is pleased to support the GMFH publishing team in bringing you this document on gut microbiota and the gut-brain axis.

We open with a summary editorial by Premysl Bercik - gastroenterologist and Associate Professor in the Division of Gastroenterology at McMaster University (Canada) - who, along with his colleagues, is carrying out leading-edge gut-brain research that investigates links between the brain, gut microbiota, and immune system. The editorial is followed by a selection of recent articles on the microbiota-gut-brain axis from the Gut Microbiota for Health website.

First, Emeran Mayer, author of a popular book called *The Mind-Gut Connection*, offers his perspective on microbes in gut-brain communication. Then we feature brief coverage of several studies showing that gut-brain communication is a two-way street, a review of a provocative hypothesis on sex hormones

and brain development, and questions that emerged at a recent event discussing developmental influences of microbiota and other hot topics related to the gut-brain axis.

When it comes to brain-related disorders, researchers are working to discover more about the role of the gut microbiota in pathophysiology. Below we feature an article providing clues about the influence of gut bacteria on depressive behaviours; and turning to mechanisms, we provide a review of the nascent study of gut bacterial metabolites as neuromediators.

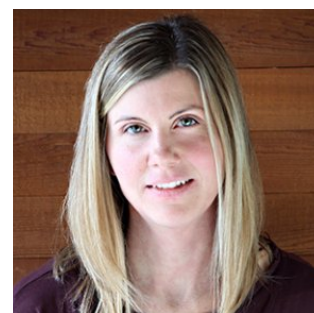
With new therapeutics, insights on the gut-brain axis could really make a difference for patients. Here we highlight a systematic review on probiotics for improving human mental health; an article on how probiotics can influence social behaviours in mice; and an article speculating on how a high-fibre diet could positively affect the brain.

Finally, in our editors' wrap-up interview with Premysl Bercik, they discuss an important question: "Can the science of the microbiota-gut-brain axis be made relevant to clinical practice?" We hope you enjoy reading on this topic - and be sure to check the GMFH website for more scientific content about the microbiota-gut-brain axis in the months ahead.

**Paul Enck**  
**Kristina Campbell**



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Science writer Kristina Campbell (M.Sc.), from British Columbia (Canada), specializes in communicating about the gut microbiota, digestive health, and nutrition. Author of the best selling *Well-Fed Microbiome Cookbook*, her freelance work has appeared in publications around the world. Kristina joined the Gut Microbiota for Health publishing team in 2014.

# TABLE OF CONTENT

EDITORIAL .....	4
SELECTED CONTENT FROM GUTMICROBIOTAFORHEALTH.COM	
• Pinpointing the role of microbes in human gut-brain communication .....	8
• Do development and maturation of the gut-brain axis differ between the sexes? .....	10
• Gut microbiota changes may be responsible for depressive-like behaviours in mice through alterations in host metabolism .....	12
• Neuromediators in the Gut-Brain Axis .....	14
• Could probiotics be used to improve human mental health? .....	15
• The potential of probiotics and diets to reverse asocial behaviours in mice that are seen in autism spectrum disorders .....	17
• Can a high-fibre diet prevent and/or treat neurological disorders? .....	19
BOOKS AND RESOURCES .....	21
INTERNATIONAL SUMMIT & ECOSYSTEM	23

# EDITORIAL



In humans, signals travel between the gut and the brain through networks of neurons in the central nervous system (CNS) and parts of the peripheral nervous system - namely, the division of the autonomic nervous system called the enteric nervous system (ENS). With approximately 100 billion neurons in the brain and 100 million in the spinal cord, the job of the CNS is to integrate sensory information and generate the behaviours needed to successfully interact with the environment. The 200-600 million neurons in the ENS - which extend, web-like, along the length of the digestive tract - react to chemical and mechanical stimuli from the gastrointestinal tract and contribute to the pool of information received by the brain. The vagus nerve (i.e. cranial nerve X) is an important channel by which information is transmitted between the digestive tract and the brain. Signals are bidirectional, but the vast majority (90%) travel upward, keeping the brain constantly informed about gut activity. This bidirectional communication between the brain's emotional and cognitive centers and peripheral intestinal functions is known as the gut-brain axis.

Clinical evidence linking the digestive tract and the brain is well known. Not only are brain and gastrointestinal diseases often comorbid, but also treatments for infection sometimes induce psychiatric side effects, as in cases of antibiotic-induced psychosis<sup>(1)</sup>. In recent years, however, knowledge about the connection between the gut and the brain has been enhanced by increased data on how the gut microbiota influence gut-brain communication.

## The microbiota-gut-brain axis

Increasing data from mice and humans show how gut microbiota influence the gut-brain axis. Germ-free mice have an abnormal response to stress, differing patterns of social interaction and exploratory behaviors, and alterations in cognition<sup>(2)</sup>, in addition to observable differences in their

brains: defective and immature microglia<sup>(3)</sup>, hypermyelinated axons in the prefrontal cortex and an upregulation of genes linked to myelination<sup>(4)</sup>, and altered formation of synapses (higher expression of synaptic-related proteins in the striatum)<sup>(5)</sup>. In addition, our lab has shown that germ-free mice or those with a severely disrupted microbiota have altered expression of the neuromodulator BDNF (brain-derived neurotrophic factor) in the hippocampus and amygdala<sup>(6)</sup>.

Human evidence for the influence of gut microbes on the brain include placebo-controlled intervention studies suggesting that modulation of the gut microbiota may produce observable changes in mood or behaviour. Several studies<sup>(7)(8)</sup> have reported that mixtures of different probiotic species can positively affect brain function in healthy individuals. One

# EDITORIAL

study to date<sup>(9)</sup> has used functional magnetic resonance imaging to observe the impact of a probiotic-containing fermented milk on brain function of healthy women; after the intervention, researchers found changes in the activity of the brain regions that control emotion and sensation. Studies like these are the first step; researchers are poised to learn much more about mechanisms that account for the apparent effects of gut microbiota on the brain.

## Early life influences

How important are gut microbiota in early life for shaping the adult brain? Results from mice show that exposing them to stress in early pregnancy changes their vaginal microbiome and, at birth, can induce changes in the offspring's gut microbiota. Potentially these changes can reprogram the offspring's brain and affect later-life behaviour<sup>(10)</sup>. Studies using mouse maternal separation as a model of early-life stress have found some of the well described reactions of mice to stress (anxiety-like behavior and behavioral despair) in adulthood only occur if the mice have a gut microbiota<sup>(11)</sup>. And several studies have now shown that some of the alterations observed in the brains and behaviours in germ-free mice can be prevented if the mice are exposed to a complex gut microbiota in early life<sup>(12)</sup>.

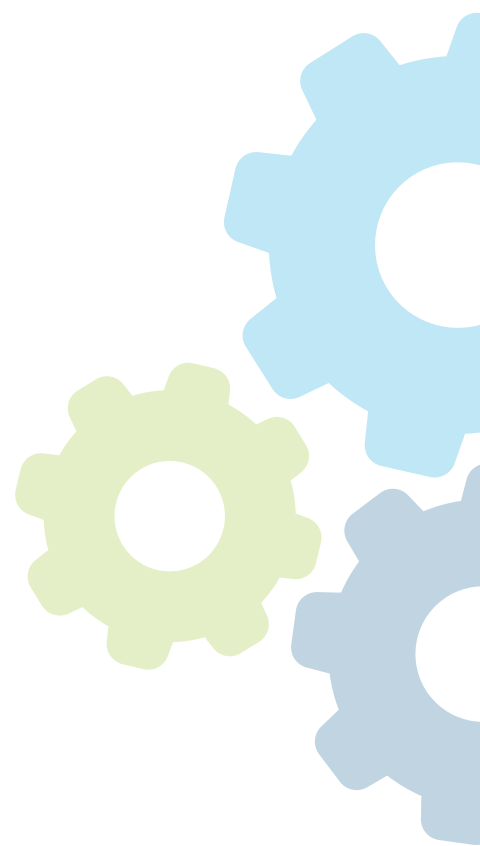
In humans it is not certain how early-life events contribute to the

establishment of a robust, diverse gut microbiota, nor how this affects long-term brain health.. However, it seems that avoiding major microbiota perturbations in the first few years of life might be required for the development of the brain to proceed uninterrupted.

## Mechanisms

Microbiota can influence gut-brain communication through neural, immune, and hormonal routes. Different kinds of bacteria appear to influence ENS neurons differently, with some exciting responses<sup>(13)</sup> and some dampening them<sup>(14)</sup>. Gut microorganisms can also influence ENS activity by affecting production of molecules, like gamma-aminobutyric acid (GABA)<sup>(15)</sup>, which act as local neurotransmitters. Immune signaling is another way the gut microbiota seems to alter messages to the brain, since evidence shows the gut microbiota can affect immune cells located in the gut mucosa that modify activity of sensory neurons of the ENS<sup>(16)</sup>. Furthermore, the gastrointestinal tract and its bacteria contribute to the body's production of hormones and neurotransmitters<sup>(17)</sup>, which affect different processes throughout the body, including those that affect the brain.

In some cases, gut-brain signalling could be initiated by metabolites - biologically active small molecules that are the products of gut bacterial metabolism. Many of the known metabolites exert their



# EDITORIAL

effects on multiple tissues and organs in the body, including the brain. Short-chain fatty acids (SCFAs) have been singled out as particularly important metabolites with possible influences on brain function<sup>(18)</sup>, but thousands of others exist. Some of them are thought to perform neuromediator and/or endocrine functions<sup>(19)</sup>, but how they work is not well understood. Learning more about these molecules is one of the keys to progress in the field of gut-brain communication.

## Links to disease

Microbial alterations are observed in a growing list of disorders involving the human brain, including autism spectrum disorder, anxiety, depression, obsessive-compulsive disorder, post-traumatic stress disorder, alcoholism, anorexia, and Parkinson's disease. The next step for each of these disorders is to go beyond associations and investigate whether or not the microbiota play a pathophysiological role. Our group, for example, recently found that transferring the microbiota of individuals with comorbid anxiety induced anxiety-like behavior in gnotobiotic mice. More studies of this kind with humanized models will advance knowledge about contributors to these brain-related disorders.

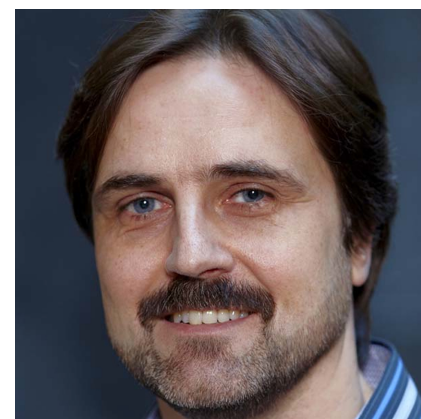
## Promising therapeutics

Despite the complexity of brain function and mental disorders in humans, and the difficulty in translating research from rodents to humans, research hints at the potential of gut microbiota alterations for influencing gut-brain axis in humans. What will really benefit patients, in health and disease, are the new therapeutic options that emerge from this area of research. A number of promising methods for modifying the gut microbiota to influence brain function in certain contexts are emerging: probiotics, prebiotics, diet, antibiotics, phages, and 'ecobiotherapy' (supplying a complete community of microbes prepared synthetically or through fecal microbiota transplantation).

## The future

Actionable advice and therapeutics in the field of the gut-brain axis are not yet a reality. We still have important questions to answer in the field, including: How do human genetics and gut microbiota together influence brain function? What are the limits of each factor's influence on the brain? Which gut bacteria or bacterial metabolites are the most influential in specific disease conditions? And how can we manipulate the gut microbiota in a lasting and beneficial way in order to change brain function?

Researchers will need to increasingly look at humanized mice to make mechanistic connections. To find ways of applying gut microbiota research in clinical settings, innovation will also be required in computational analyses, and methodologies including culture based profiling, allowing rapid integration of large amounts of data. Gut microbiota is enabling new perspectives on the modifiability of the gut-brain axis with the potential to optimize brain health—and we are only at the beginning of the journey.



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McMaster University (Canada)

# EDITORIAL

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## Pinpointing the role of microbes in human gut-brain communication

Published in DIGESTIVE HEALTH, GUT BRAIN AXIS, GUT MICROBIOTA  
Written on August 3, 2016 by Kristina Campbell



*Science writer Kristina Campbell (M.Sc.), from British Columbia (Canada), specializes in communicating about the gut microbiota, digestive health, and nutrition. Author of the best selling Well-Fed Microbiome Cookbook, her freelance work has appeared in publications around the world. Kristina joined the Gut Microbiota for Health publishing team in 2014.*

When Michael Gershon called the digestive system “the second brain” in his 1999 book, it was because scientists were beginning to realize that the gut and the brain in humans were engaged in constant conversation. Emeran Mayer, a leading researcher in the field of the gut-brain axis, affirms that this connection has been known for years. “Gut-brain communication is firmly established. There’s no question,” Mayer says in an interview with GMFH editors. “There’s extensive animal data and clinical observations: if you feel stressed you will feel the effects in your gut, if you feel anxious you notice the butterflies in your stomach, if you’re depressed, you may develop constipation.”

Mayer, a gastroenterologist who encountered many patients in his career with curious constellations of gut-brain symptoms, became preoccupied with finding out the how this back-and-forth messaging occurs. He had more questions than answers in his clinical practice, but a breakthrough came when more data began to emerge on the microbiome.

“I’ve spent my entire career studying brain-gut interactions,” says Mayer. “Only in the last five years I’ve included the microbiome in our studies.” He notes that this new angle is starting to advance scientists’ understanding of how gut-brain communication occurs—both from the bottom up and from the top down—and the

consequences of disruptions in this communication.

Mayer has authored a new book, *The Mind-Gut Connection*, aimed at covering gut-brain communication for a lay audience. In it, he emphasizes the role of the gut microbes and the many aspects that require more investigation in human populations. He says that, remarkably, the gut microbiota during certain periods in life may set the framework for subsequent patterns of gut-brain communication.

“Almost certainly the most important effects happen early in life, starting prenatally and in the first three years when the microbes, as well as the basic brain circuit[s],

“Mayer has authored a new book, *The Mind-Gut Connection*, aimed at covering gut-brain communication for a lay audience.”



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## Pinpointing the role of microbes in human gut-brain communication

are being assembled and become adult-like,” Mayer says.

Mayer says knowing that microbes play a part in gut-brain communication—and indeed, in many other aspects of brain health and function—necessitates a new approach in medicine. “The book makes the case for a new ecological view of health and disease,” he says. “Such a new view is essential if we want to strive for optimal health and not just prevention or treatment of disease.” At the end of his book, Mayer provides suggestions on how to improve health by targeting the gut microbiome, like limiting animal fat and consuming more fermented foods and probiotics.

In Mayer’s gastroenterology practice, he sees many who could benefit from new microbiome-based therapeutic approaches to both gastrointestinal and brain disorders, yet he currently advises caution. He says, “We’re really just beginning to understand what a healthy microbiome is, and how it is altered in different diseases. I think in five years we’ll know a lot more, and may be able to use our knowledge about the gut microbiome for diagnosis, prediction of treatment outcomes and for the development of new therapies.”

“Such a new view is essential if we want to strive for optimal health and not just prevention or treatment of disease.”



**Source:**

Mayer E. **The Mind-gut connection: How the hidden conversation within our bodies impacts our mood, our choices, and our overall health.** New York, NY: Harper Wave; 2016.



**Read the original post online at:**

<http://www.gutmicrobiotaforhealth.com/en/pinpointing-role-microbes-human-gut-brain-communication/>

# SELECTED CONTENT

## Do development and maturation of the gut-brain axis differ between the sexes?

Published in GUT BRAIN AXIS

Written on March 28, 2016 by Andreu Prados



*Andreu Prados holds a Bachelor of Science Degree in Pharmacy & Human Nutrition and Dietetics. Science writer specialised in gut microbiota and probiotics, working also as lecturer and consultant in nutrition and healthcare.*

**A recent review, published by postdoctoral researcher Dr. Eldin Jasarevic from the Department of Animal Biology in the University of Pennsylvania, argues that sex differences influence the development, maturation, and maintenance of the gut microbiome-brain axis throughout the lifespan.**

The gut-brain axis (GBA) involves bidirectional communication between the central and enteric nervous systems, which facilitates the integration of peripheral and central immune, metabolic, and endocrine signals. Recent advances have described the importance of gut microbiota in influencing these interactions. The formation of the gut-brain axis begins immediately following colonization by microbial communities that reside within the birth canal. Sex-specific maturation of the gut, hormones, and brain occur in parallel across the lifespan. Shifts in structure and function of the gastrointestinal tract and brain provide windows of opportunity for intervention during distinct life stages.

Existing evidence from studies both in animals and humans supports that during the prenatal period, the metabolic demand of male and female foetuses on the mother differs, and the maternal gut microbiome orchestrates nutritional status during development. For instance, during the first trimester

there is a rise in short chain fatty acid (SCFA) - producing microbiota, which suggests a role for maternal-derived microbial substrates in foetal neurodevelopment. However, there is a vast expansion of bacterial diversity during late gestation when oestrogens are at maximal peak and SCFA exposure decreases in order to meet the offspring's increased nutritional and metabolic demands. During the postnatal period, microbial colonization may influence sex differences in immunocompetent cells' maturation and function in the brain. Environmental perturbations such as stress during critical windows of development influence gut-brain signalling and are linked to metabolic reprogramming of the offspring gut and brain. Sex differences in the gut microbiome emerge during puberty and continue into adulthood. Puberty is a period of increased sex-specific risk for stress, which could affect later-life behaviour and anxiety. Likewise, the researchers suggest that gut microbial communities may alter host hormones and affect

# SELECTED CONTENT

## Do development and maturation of the gut-brain axis differ between the sexes?

neurotransmitters that are critical for normal communication between the gut and brain. In adulthood, gut microbiota are more stable and appear better adapted to environmental challenges. Interestingly, sex may determine risk for negative symptoms related to gut health. Indeed, gender bias in autoimmunity is influenced by microbiota. For instance, sex-specific changes on gut physiology and gut microbiota composition can explain, at least in part, the increased female risk for autoimmune disorders and allergies.

In conclusion, microbial communities contribute to several physiological processes throughout the lifespan. Sexually dimorphic communication between the gut microbiome and the brain occurs in parallel to immune, metabolic and neural changes, which suggests that sex-specific transitions could be considered in health and disease states.

“Interestingly, sex may determine risk for negative symptoms related to gut health.”



**Source:**

Jasarevic E, Morrison KE, & Bale TL. **Sex differences in the gut microbiome-brain axis across the lifespan.** *Philos Trans R Soc Lond B Biol Sci.* 2016; 371(1688):20150122. doi:10.1098/rstb.2015.0122.



**Read the original post online at:**

<http://www.gutmicrobiotaforhealth.com/en/development-maturation-gut-brain-axis-differ-sexes/>

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## Gut microbiota changes may be responsible for depressive-like behaviours in mice through alterations in host metabolism

Published in ANXIETY & DEPRESSION, DYSBIOSIS  
Written on June 29, 2016 by Paul Enck



*Prof. Dr. Paul Enck, Director of Research, Dept. of Psychosomatic Medicine and Psychotherapy, University Hospital Tübingen, Germany. He is board member/treasurer of the European Society of Neurogastroenterology and Motility and of the German Society of Neurogastroenterology and Motility, and has served as reviewer for many international journals and grant agencies.*

**A recent study, led by Dr. Peng Xie from the Chongqing Medical University in China, has demonstrated that intestinal ‘dysbiosis’ may have a causal role in the development of depressive-like behaviours in mice through altering host metabolism.**

It has been previously described that the gut microbiota may be an environmental factor that can modulate brain physiology through the microbiota-gut-brain axis. Zheng and colleagues have demonstrated that the absence of gut microbiota in germ-free (GF) mice led to a decreased depression-like behaviour as evidenced by a significantly decreased immobility time in the forced swimming test—used as an index of depression-like behaviour—compared with their conventionally raised specific pathogen-free (SPF) counterparts. These results suggest a link between the microbiota-gut-brain axis and depression-like behaviour.

In addition, the researchers showed that patients with major

depressive disorder (MDD) (n= 58) exhibited significant alterations in their gut microbiota relative to healthy controls (n = 63). Decreased microbial diversity in MDD patients were characterized by alterations in the relative abundances of the phyla Firmicutes, Actinobacteria and Bacteroidetes. However, these results are not consistent with a previous study by Jiang et al. in which increased faecal bacterial diversity was found in the active-MDD vs. the healthy control group but not in the responded-MDD vs. the healthy control group. Bacteroides, Proteobacteria, and Actinobacteria increased in level, whereas that of Firmicutes was reduced in MDD groups compared with the healthy control group.

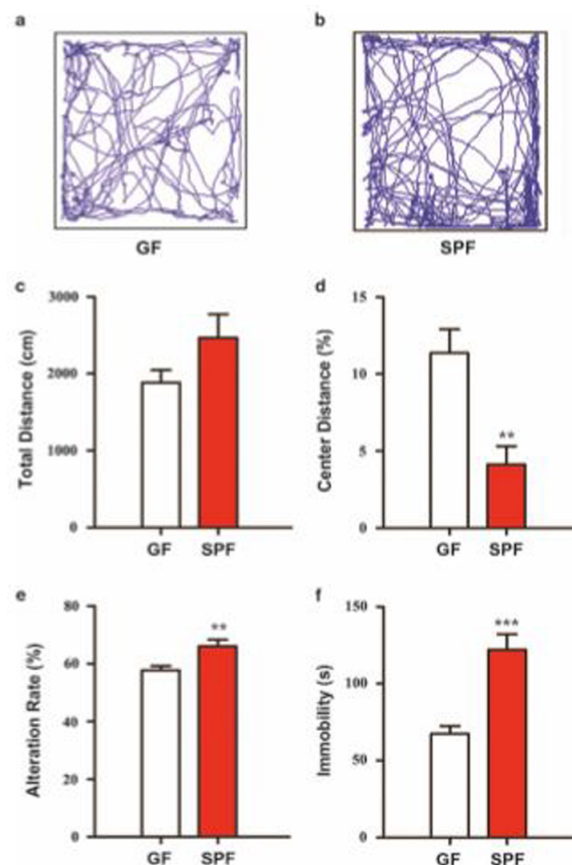
“Decreased microbial diversity in MDD patients were characterized by alterations in the relative abundances of the phyla Firmicutes, Actinobacteria and Bacteroidetes.”

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## Gut microbiota changes may be responsible for depressive-like behaviours in mice through alterations in host metabolism

When mice were transplanted the microbiota of MDD patients (n=5) this induced depression-like behaviours in GF recipient mice, while transplantation of the microbiota of healthy controls (n=5) did not induce such behavioural changes. Characteristics of the gut microbiota responsible for distinguishing depressed from healthy humans were also observed in recipient mice. The mice harbouring the gut microbiota from MDD patients exhibited disturbances of microbial genes and host metabolites involved in carbohydrate and amino acid metabolism. These results demonstrate that the role of gut microbiota in the development of depressive-like behaviours may be mediated through alterations in the host's metabolism.

In sum, gut microbiota can contribute to depression-like behaviour in mice through altering host metabolism. These findings, if found to be applicable to humans, could provide a new approach for depression therapies.



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### Source:

Zheng P, Zeng B, Zhou C, et al. **Gut microbiome remodeling induces depressive-like behaviors through a pathway mediated by the host's metabolism.** *Molecular Psychiatry.* 2016; 1-11. doi: 10.1038/mp.2016.44.



### Read the original post online at:

<http://www.gutmicrobiotaforhealth.com/en/gut-microbiota-changes-may-responsible-depressive-like-behaviours-mice-alterations-host-metabolism/>

# SELECTED CONTENT

## Neuromediators in the Gut-Brain Axis

Published in GUT BRAIN AXIS

Written on March 11, 2016 by Boris Shenderov



*Dr. Boris Shenderov is a professor of microbiology who conducts research at the G.N. Gabrichevsky Moscow Research Institute of Epidemiology and Microbiology. He has authored more than 500 scientific papers and abstracts throughout his career.*

It is increasingly clear that brain processing is influenced by the gastrointestinal microbiota; study of the gut-brain axis has shown evidence that gut bacteria interact with the enteric nervous system and the central nervous system. Good brain function depends on neuromediators – that is, substances that carry messages between neurons, or from a neuron to another type of cell.

Could an increased understanding of neuromediators be the key to unlocking how the gut and the brain influence each other?

This review paper by Russian researchers Oleskin, El'-Registan, and Shenderov describes how microorganisms engage in collective activities (likened to “social behavior”), how they exchange information (or “communicate”), and how they form associations composed of many individual cells (“biosocial systems”). Cell coordination in various microbial biosocial systems such as colonies and biofilms depends on the microbes’ chemical contact and physical interaction. This review focuses on aspects of chemical communication.

Evidence suggests an important role for neuromediators in microbial communication, both within and between species. In Table 1 of this review article, authors describe the effects (and/or associations) of neuromediators, from catecholamines to nitric oxide, on microbial populations. Table 2 outlines the production of neuromediators by different bacterial species. These communicative activities of microbes may prove to have measurable effects on brain function. In the future, this information may be used in the development of new probiotic preparations that have a targeted neurochemical effect.



### Source:

Oleskina AV, El'-Registanb GI, Shenderov BA. **Role of Neuromediators in the Functioning of the Human Microbiota: “Business Talks” among Microorganisms and the Microbiota-Host Dialogue.** Microbiology 2016; 85(1): 1-22.



### Read the original post online at:

<http://www.gutmicrobiotaforhealth.com/en/neuromediators-gut-brain-axis/>

# SELECTED CONTENT

## Could probiotics be used to improve human mental health?

Published in ANXIETY & DEPRESSION, PROBIOTICS  
Written on August 26, 2016 by Andreu Prados



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Recent advances in research have described the importance of gut microbiota in influencing interactions between the central and the enteric nervous systems. These brain-gut interactions appear to be bidirectional by means of neural, endocrine, immune, and humoral signals. Most of the data have been acquired using rodents (mice or rats) and pigs.

Evidence of microbiota-mental health interactions comes from the association of intestinal dysbiosis with central nervous system disorders (e.g. anxiety-depressive behaviours) and functional gastrointestinal disorders (e.g. irritable bowel syndrome) with mental health comorbidities.

Few human studies assessing the effect of probiotic supplementation on mental health through modulation of brain-gut pathways have been conducted to date. However, a recent systematic review of 38 randomized controlled trials in both animals and humans (25 were in animals, 15 in humans and 2 studies were conducted in humans and animals), led by Prof. Paul Enck from the Department of Psychosomatic Medicine and Psychotherapy at University Hospital Tübingen in Tübingen (Germany), has concluded that probiotics could be effective in improving psychiatric disease-associated functions and memory abilities. The paper by Wang, et al. found probiotics that showed efficacy in improving psychiatric disorder-related behaviours (anxiety, depression, mood, stress response) and memory

abilities (including spatial and non-spatial memory) included Bifidobacterium (*B. longum*, *B. breve*, and *B. infantis*) and Lactobacillus (*L. helveticus*, *L. rhamnosus*, *L. plantarum*, and *L. casei*). Doses between 10<sup>9</sup> and 10<sup>10</sup> colony-forming units (CFU) for durations of 2 weeks in animals and 4 weeks in humans showed sufficient effects. Although translations of animal studies to human studies suggest possibilities, further studies are worthwhile, especially in patients with mental diseases that usually show gastrointestinal comorbidities. In addition to behavioural measurements such as psychological questionnaires or scales, more neuroimaging studies in humans are needed in order to study what area is altered in the brain that causes behavioural changes after the consumption of probiotics.

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## Could probiotics be used to improve human mental health?

On the other hand, a recent systematic review of 10 randomized controlled trials in humans (including 6 trials that were also included in the Wang, et al. systematic review), led by Dr. Paul Ritvo from York University in Toronto, Ontario (Canada), provides limited support for the use of probiotics in reducing anxiety-depressive symptoms in humans. Although it seems that probiotic supplementation could lead to psychological benefits, substantial methodological limitations were found as the main problem in generalizing its findings. The researchers emphasized that further follow-up intervention studies are needed in order to better understand the potential human mental health benefits of probiotic supplementation.

One of many possible mechanisms that could explain the role of gut microbes in affecting brain function is through modulating the level of microbial producers and

consumers of gamma-aminobutyric acid (GABA). In this context a noteworthy and important step forward is the recent identification of a species of gut bacteria, called KLE1738, which can only grow in the presence of gamma-aminobutyric acid (GABA). KLE1738 is a newly discovered human gut bacterium that may have an unusual metabolism that is based on consuming GABA, the major inhibitory neurotransmitter of the central nervous system. Other mechanisms involving serotonin-producing bacteria could also have equal potential relevance for depression and other mood disorders.

On the whole, current research supports the idea that microbial communities in the gut may play an important role in mental health. Further human studies in this area are needed in order to elucidate which patients could benefit from probiotic supplementation for improving their mental function.

“On the whole, current research supports the idea that microbial communities in the gut may play an important role in mental health.”



### Source:

Pirbaglou M, de Souza RJ, Stearns JC, Motamed M, Ritvo P. **Probiotic supplementation can positively affect anxiety and depressive symptoms: a systematic review of randomized controlled trials.** Nutr Res. 2016, doi:10.1016/j.nutres.2016.06.009.

Wang H, Lee IS, Braun C, Enck P. **Effect of probiotics on central nervous system functions in animals and humans - a systematic review.** J Neurogastroenterol Motil. 2016, doi: 10.5056/jnm16018.



### Read the original post online at:

<http://www.gutmicrobiotaforhealth.com/en/probiotics-used-improve-human-mental-health/>



# SELECTED CONTENT

## The potential of probiotics and diets to reverse asocial behaviours in mice that are seen in autism spectrum disorders

Published in *AUTISM, GUT BRAIN AXIS, GUT MICROBIOTA*  
Written on September 5, 2016 by Andreu Prados



*Andreu Prados holds a Bachelor of Science Degree in Pharmacy & Human Nutrition and Dietetics. Science writer specialised in gut microbiota and probiotics, working also as lecturer and consultant in nutrition and healthcare.*

It has been previously suggested that a high-fibre diet can prevent neurodegeneration by increasing gut microbiota derived butyrate in the colon, but how changes in gut bacteria could influence brain development and function is still poorly studied.

A recent study, led by Dr. Mauro Costa-Mattioli from the Baylor College of Medicine in Houston, Texas (USA), has found that the reintroduction of a commensal bacterial strain can reverse asocial behaviours in mice that are seen in autism spectrum disorders (ASDs).

Previous human epidemiological studies that have found that maternal obesity during pregnancy could increase children's risk of neurodevelopmental disorders, including ASDs. Besides this, recurrent gastrointestinal problems are frequently reported in individuals with ASDs. Based on these observations, the researchers sought to explore the connections between changes in diet, the gut microbiome, and social behaviours.

First of all, female mice were fed either a regular diet (RD, consisting of 13.4% kcal from fat, 30% kcal from protein, and 57% kcal from carbohydrates) or a high-fat diet (HFD, consisting of 60% kcal from fat, 20% kcal from protein, and 20% kcal from carbohydrates) for 8 weeks. Females then were paired with males to produce offspring that all were given RD after weaning. Maternal high-fat diet (MHFD) significantly increased maternal

weight. At 7-12 weeks of age behavioural and electrophysiological experiments were performed in order to study social behaviour in maternal regular diet (MRD) and maternal high-fat diet offspring. Maternal high-fat diet offspring displayed impaired sociability and dysbiosis of the gut microbiota.

Buffington and colleagues next tested whether the gut microbiota mediated MHFD-induced social deficits. To this end, at 3 weeks an MHFD mouse was co-housed with three MRD mice. As a result, co-housing MHFD with MRD offspring rescued both social dysfunction and the microbiota phylogenetic profile of the socially impaired mice born to mothers on a high-fat diet. Taken together, these data indicate that gut microbiota mediates MHFD-induced social deficits and suggest that MHFD offspring may lack one or more beneficial bacterial species required for normal social behaviour.

# SELECTED CONTENT

## The potential of probiotics and diets to reverse asocial behaviours in mice that are seen in autism spectrum disorders

Faecal transplant experiments in germ-free mice suggested that dysbiosis of the gut microbiota in the mice born to mothers on a high-fat diet could be involved in their social deficits.

In order to elucidate the specific bacterial species involved in social deficits of the mice, the researchers performed metagenomic sequencing of faecal samples from both MHFD and MRD offspring. *Lactobacillus reuteri* was the most drastically reduced in the gut microbiota of mice born to mothers on the high-fat diet.

In the high-fat-diet fed offspring, elective reintroduction of *L. reuteri* originally isolated from human breast milk restored the social deficits in the mice-but not repetitive behaviours and anxiety- and it also restored levels of oxytocin, a hormone that plays a crucial role in social behaviours and has been associated with autism in humans.

The reward circuitry in the socially impaired mice was also assessed. According to Dr. Costa-Mattioli, "in response to social interaction there was a lack of synaptic potentiation in a key reward area of the brain that could be seen in the normal control mice." It is noteworthy that the reintroduction of *L. reuteri* in the maternal-high-fat-diet offspring also restored the changes in synaptic function in the reward circuitry.

On the whole, a maternal high-fat diet may lead to dysbiosis of the gut microbiota of offspring and induce behavioural alterations that can be restored via selective reintroduction of *L. reuteri*.

Based on the hypothesis that changes in the gut microbiota may be relevant to the development of behavioural symptoms associated with ASD, interventional studies are currently being developed. For instance, a pilot study that is currently underway, led by Dr.

Filippo Muratori from the IRCCS Stella Maris Foundation and University of Pisa, aims to explore supplementation with a probiotic mixture in pre-schoolers with ASD. As some ASD patients may have some gastrointestinal problems that may be associated with a higher rate of irritability, aggressive behaviours and sleep disturbances, therefore the treatment of these symptoms with probiotics opens a new therapeutic approach in ASD. Intervention studies in humans are warranted to develop evidence-based guidelines for the use of probiotics as a non-pharmacological option complementary to the recommended treatments for ASD, which are based on an integrated approach including behavioural treatments, drugs and other options.



### Source:

Buffington SA, Di Prisco GV, Auchtung TA, et al. **Microbial reconstitution reverses maternal diet-induced social and synaptic deficits in offspring.** *Cell.* 2016; 165(7):1762-75. doi:10.1016/j.cell.2016.06.001.

Santocchi E, Guiducci L, Fulceri F, et al. **Gut to brain interaction in Autism Spectrum Disorders: a randomized controlled trial on the role of probiotics on clinical, biochemical and neurophysiological parameters.** *BMC Psychiatry.* 2016; 16:183. doi:10.1186/s12888-016-0887-5.



### Read the original post online at:

<http://www.gutmicrobiotaforhealth.com/en/potential-probiotics-diets-reverse-asocial-behaviours-mice-seen-autism-spectrum-disorders/>

# SELECTED CONTENT

## Can a high-fibre diet prevent and/or treat neurological disorders?

Published in FIBERS, FOOD & INGREDIENTS  
Written on March 23, 2016 by Andreu Prados



*Andreu Prados holds a Bachelor of Science Degree in Pharmacy & Human Nutrition and Dietetics. Science writer specialised in gut microbiota and probiotics, working also as lecturer and consultant in nutrition and healthcare.*

In recent years, interest has grown in how diet influences brain function through the gut microbiome, yet the topic is still largely understudied. A recent review article, led by Dr Rajiv R. Ratan from the Brain and Mind Research Institute (BMRI) in New York, explores the provocative idea a high-fibre diet can prevent neurodegeneration in the brain by increasing butyrate in the colon.

Diet-derived substrates impact bacterial community structure and metabolism in the colon. Short-chain fatty acids (SCFAs) formed by microbial fermentation have an important effect on both colonic and systemic host health. Butyrate in particular is primarily synthesized through the fermentation of resistant starch (e.g. tubers) and fructo-oligosaccharides (FOS) (e.g. bananas and asparagus) by bacteria in the colon. Butyrate can also be produced in lower concentrations by mammalian cells and can be found in plant oils and animal fats (e.g. butter is the richest dietary source of butyrate).

Butyrate is a molecule with a wide range of biological functions, which makes it attractive for therapeutic purposes. It has been shown to exert direct effects upon gene

expression in mammalian cells through histone deacetylase inhibition, although this effect is not specific to histone proteins alone. It is a potential therapeutic for neurological diseases, as many common neurological diseases show reduced histone acetyltransferase (HAT) activity. Sodium butyrate (NaB) has demonstrated neurotrophic effects in mouse models of Parkinson's disease, in cisplatin-induced hearing loss, and in cases of disease-associated or toxicity-induced dementia, such as Alzheimer's disease. These effects result in an improvement of behavioural outcomes, including learning and memory, which can be explained by the up-regulation of genes involved in promoting cell survival, plasticity and regeneration.

# SELECTED CONTENT

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Furthermore, butyrate can assist as an energy metabolite to produce adenosine triphosphate (ATP). It serves as a preferred energy source for colonocytes and the researchers of this review hypothesize that if sufficient butyrate levels could be reached in the brain, it could be used as an energy substrate, as in the colon. This would be an important outcome, as energy dyshomeostasis occurs in the brain in many neurological diseases (e.g. in Alzheimer's, the brain has reduced glucose utilization from the earliest stages of the disease). Aside from its metabolic effects, butyrate might help to rectify the disease-associated mitochondrial dysfunction in the brain secondary to reduced brain glucose availability.

Last, but not least, butyrate can act as a G protein-coupled receptor (GPCR) activator. Some GPCRs have been identified as receptor targets for SCFAs. Strikingly, butyrate induces anti-inflammatory effects through activation of GPR109a, which is a kind of GPCR expressed

in colonocytes, T cells, and microglia. It is thought that this receptor could be a good target for therapeutics in Parkinson's disease.

Available data shows a strong connection between the gut microbiota, butyrate and the brain. According to a study performed in mouse models, either butyrate-producing bacteria or an oral gavage of NaB can restore blood-brain barrier permeability in germ-free mice. Also, mice fed a diet high in fermentable fibre recover faster and show attenuated neuroinflammation after exposure to lipopolysaccharide. Taking these data together, the authors hypothesize that the elevated butyrate from the dietary fibre fermentation may contribute to both the beneficial neurological and immune effects on host health.

Regarding human populations, the beneficial effects of a high-fibre diet on memory and cognition are starting to be explored. Several studies show that probiotics could

lower psychological stress in healthy human subjects and in subjects with chronic fatigue syndrome by increasing butyrate-producing bacteria. However, elevated SCFAs in the bloodstream due to increased gut permeation by abnormal microbiota may be unfavorable for children with autism spectrum disorders.

In conclusion, a high-fibre diet is hypothesized to prevent and/or treat brain disorders by elevating butyrate in the gut. More research is needed in order to elucidate the possible pharmacological beneficial effect of butyrate on brain disorders, including neurodegenerative diseases and psychological disorders.



### Source:

Bourassa MW, Alim I, Bultman SJ, Ratan RR. **Butyrate, neuroepigenetics and the gut microbiome: can a high fiber diet improve brain health?** *Neurosci Lett.* 2016; doi:10.1016/j.neulet.2016.02.009.



### Read the original post online at:

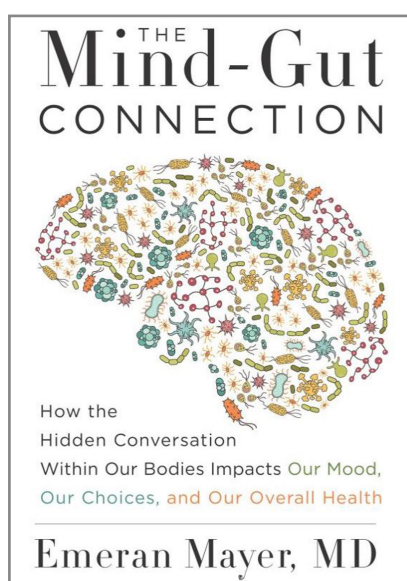
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# BOOKS & RESOURCES

## Connecting the Dots between Digestion and Emotion: Book Review of Emeran Mayer's The Mind-Gut Connection

Published in GUT BRAIN AXIS

Written on August 3, 2016 by Kristina Campbell



Emeran Mayer

Digestion and emotion have long been treated separately in medicine and science, like dots far apart on a map. Despite the phrase “gut feeling” that implicitly connects the belly and the brain, the reality is that gut physiology, microbes, and the mind have all been studied independently. It’s why, when you walk into a doctor’s office complaining of both constipation and a low mood, you might have two different conversations and get two different prescriptions.

In his new book, *The Mind-Gut Connection*, gastroenterologist and University of California Los Angeles (UCLA) professor of medicine Dr. Emeran Mayer starts to skillfully draw lines between these far-apart dots. Mayer uses the book to explain the different ways the gut and the brain communicate, emphasizing the nascent science on the important role played by the gut microbiota.

Mayer’s genuine curiosity about his patients is what seemed to lead him into a career of research focused on the gut-brain axis. He took seriously the patients who came into his office with bizarre-sounding stories—sudden, unexplained vomiting in the mornings; extreme anxiety about toxic waste in the colon. The book is the product of his lifelong drive to find out more.

In the first part of the book, Mayer explains in patient detail how messages

travel both upward and downward (though mostly upward) between the digestive system and the brain. The messages are sent in various ways: hormones, the vagus nerve “information highway”, and certain signaling molecules of immune cells. One chapter is dedicated to “microbe-speak”—the gut microbiota’s contribution to gut-brain communication. One major way that gut microbes respond to constant incoming information about their host’s emotional state and stress level, it seems, is by adjusting their production of metabolites.

Next, the book explores how interactions between the mind and gut microbiome can inform everyday emotional experiences. Here Mayer makes much of the influence of early-life events on the gut-brain dialogue, an idea supported by fascinating research done in mice. He even speculates that research might reveal a key role for the gut microbiota in determining how

# BOOKS & RESOURCES

## Connecting the Dots between Digestion and Emotion: Book Review of Emeran Mayer's *The Mind-Gut Connection*

“Dietary differences may even shape gut-brain communication: for example, chapter nine outlines the compelling evidence for the mechanisms by which high-fat diets could harm the brain.”

long and how intense our emotions become on a daily basis.

The third part of the book is about optimizing brain-gut health. Mayer explains how diet plays a role in shaping the gut microbiota; he draws from research in cultural groups that have dramatically different diets from a typical person in North America. Dietary differences may even shape gut-brain communication: for example, chapter nine outlines the compelling evidence for the mechanisms by which high-fat diets could harm the brain. The book turns then to the need to rediscover the Mediterranean diet as well as beneficial fermented foods.

Recommendations are offered in a final chapter; some are based on evidence and others (like eating organically grown foods) seem to feature distinctly Californian concerns. But all of the exhortations resonate—for example, “enjoy meals together” is a good reminder to today’s fast-living families.

In *The Mind-Gut Connection*, Mayer has a good handle on the science in a realm where sticking to the facts is not an easy task. Much easier would have been to draw careless lines between the dots with a Sharpie, and then (as others do) try to sell the resulting picture.

In this first popular book to give a scientifically balanced view of how gut microbes contribute to gut-brain communication, Mayer’s main strength is his restraint. He doesn’t claim to have a miracle cure for depression or panic attacks. But he does report that when encountering patients who suffer from these conditions, he takes the time to explain the connections between what they feel in their minds and what they experience in their bodies. And it seems to give them a pocketful of validation, of hope. Things small, but not trivial.



#### Source:

Mayer E. **The Mind-gut connection: How the hidden conversation within our bodies impacts our mood, our choices, and our overall health.** New York, NY: Harper Wave; 2016.



#### Read the original post online at:

<http://www.gutmicrobiotaforhealth.com/en/connecting-dots-digestion-emotion-book-review-emeran-mayers-mind-gut-connection/>

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## ACCEPTANCE NOTIFICATION:

**February 10, 2017**

*Abstracts will peer reviewed and  
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The Gut Microbiota for Health initiative has been created by the Gut Microbiota and Health Section of the European Society for Neurogastroenterology & Motility (ESNM), member of United European Gastroenterology (UEG).  
It's mission is to promote the knowledge about gut microbiota and its effects on human health among scientists and healthcare professionals.



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