Fact sheet: Dementia and gut health

The gut-brain communication

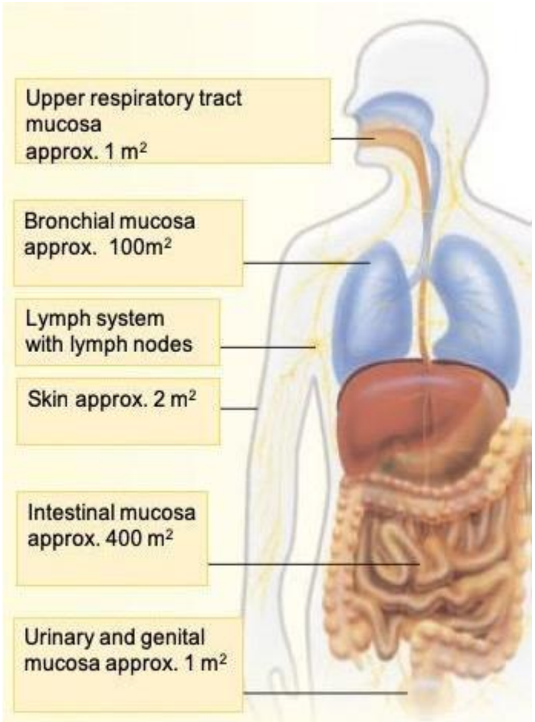
Introduction

The intestine - more than just a "digestive tube”

"Health begins in the intestines" - this insight is already described in the 4000-year-old writings of Ayurvedic medicine. The intestine is the centre of well-being. A disturbed digestive system is considered the main cause of chronic diseases.

It is well known that the intestine, as the digestive organ, transforms food and beverages into vital nutrients, supplies the body with energy and excretes food residues and unwanted substances. But that is by no means all. With a total surface area of approximately 400-600 m^2, the intestinal mucosa forms the largest interface between the organism and the outside world. Nowhere else in the body is there more intensive contact with foreign substances than in the intestine. The "dark, warm brew" of food pulp and mucus contains not only healthy nutrients but also dangerous germs. The intestinal mucosa is therefore in constant contact with potential pollutants.

This means that the intestine has a vital dual function: it must be permeable to nutrients, but at the same time, prevent the penetration of bacteria, pollen, food allergens, fungi, viruses and other foreign substances. Here it becomes clear how important an intact intestinal mucosa is for the health of the entire body. If the protective function of the mucous membrane is disturbed, the organism and especially its immune system is



overtaxed with large amounts of pathogens and harmful substances (consequences: see "Leaky gut syndrome").
For this reason, the intestinal wall needs an extremely powerful protective barrier so that anything that could cause damage does not penetrate the intestinal wall and enter the bloodstream unhindered.
The large surface area facing the "inner environment" of the intestinal lumen is protected by a multi-layered mucus layer and an effective intestine-associated immune system, the so-called GALT (**gut intestine-associated lymphatic tissue**). It is organized along the mucous membrane of the small intestine, especially in the ileum[1] area, in numerous lymph nodes, the so-called Peyer's plaques. The intestine is the largest immune organ of the body. 70-80 % of all cells that produce antibodies are located in the mucosa of the intestine. Additional protection against infection is provided by the production of the body's own bacteria-killing proteins, the defensins[2] , which are found in high concentrations in the intestinal mucosa.

Microorganisms and definitions

The research on microorganisms, i.e. bacteria, viruses, fungi etc., which inhabit the human body has developed rapidly in recent years. This scientific progress has been accompanied by misunderstandings in the use of the vocabulary used to describe these communities and their environment. A quick search on the Internet for the words microbiota or microbiome, for example, can lead to the same results. In the following we try to clarify this:

- **Microbiota:** The assemblage of microorganisms (by type) present in a defined environment. Refers to the taxonomy (name) of microorganisms.

[1] The ileum (ileum) is about three meters long and is the last part of the three sections of the small intestine. This is the only place where, for example, vitamin B12 is absorbed.
[2] Defensins are also used to defend against fungi and toxins and to inhibit viruses, they also have an antimicrobial effect.

- **Microbiome:** This term refers to the entire habitat, including the microorganisms, their genomes (i.e., genes), and the surrounding environmental conditions. This definition is based on that of "biome," the biotic and abiotic factors of given environments.
- **Metagenome:** The collection of genomes and genes from the members of a microbiota. This collection is obtained through laboratory sequencing of DNA extracted from a sample (a process called *metagenomics*).

Unfortunately, the terms microbiota and microbiome are not always used according to their definition in general language, including in science, and often overlap.

The gut microbiota

Microbes are found throughout the human body and the majority of metabolites in human plasma are microbe-derived. The alimentary tract is one of the largest interfaces between the host and the external environment: it can be considered as a continuation of the external environment in the human body. It holds the most significant population of microbes within the human body: it is inhabited by nearly 10^{14} microorganisms from at least 1000 distinct microbial species (consisting mainly of bacteria, and also fungi and virus) which are collectively known as gut (or intestinal) microbiota.

Gut microbiota is a complex system of microorganisms showing an unequal distribution from the mouth to the anus and covering several biological functions. Overall, it is composed of viruses, bacteria, yeasts and protozoa, all living (hopefully) in relative harmony. Gut microbiota composition may vary among healthy and unhealthy individuals. In healthy subjects, gut microbiota live in **eubiosis**, meaning maintaining diversity, richness and relative abundance. In this way, gut microbiota and host co-exist in a cooperative systemic aggregation model, both contributing to regulation of the barrier effect, metabolism, immunocompetence and tolerance and influencing synthesis of many substances including neurotransmitters, drug metabolism and even behaviour conditioning.

However, many factors such as:

- massive use of antibiotics,
- the prolonged use of drugs that inhibit gastric acid production (e.g. proton pump inhibitors)
- impairment of the immune system,
- alteration of the integrity of the gut mucosal barrier,
- dietary compounds

are able to alter eubiosis leading to a pathological condition called **dysbiosis**. Dysbiosis is a microbiota imbalance which in turn is strongly related to the occurrence of both GI or extra-GI diseases, including neurological disorders, through the promotion of a pro-inflammatory status.

Germ-free animal experimentation (animals are grown without microbiota, i.e., they have no microbes in their guts) is one of the most important *in vivo*[3] experimental models for studies on gut microbiota interactions. We can observe how the body is affected in the absence of microbiota, especially how this condition influences brain function and behaviour. The results of animal studies using germ-free mice point to the key role of gut microbiota in early brain development and adult neurogenesis.

Gut microbiota composition

The composition of the microbiota differs in various regions of the digestive tract. *Lactobacillaceae, Clostridum, Streptococcus Bacteroides, Actinomycinae, Corynebacteria* dominate in the small intestine, while the colon is colonized by *Bacteroides, Clostridum, Bifidobacterium* and *Enterobacteriaceae*.

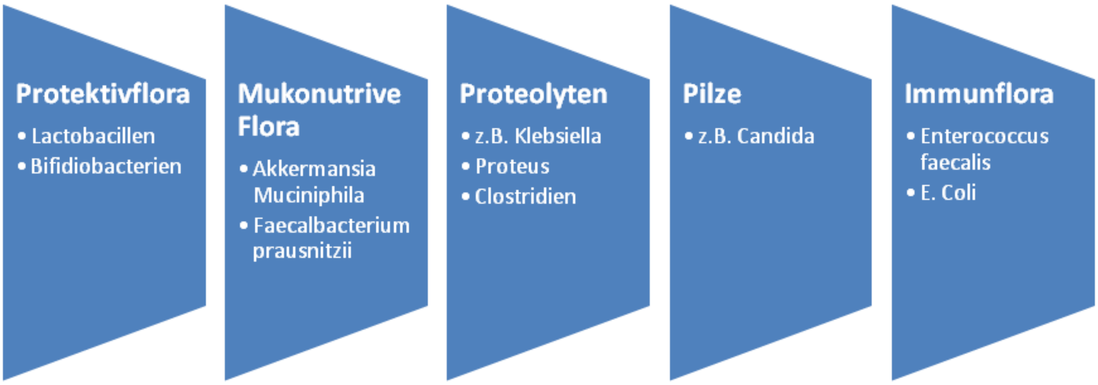


Figure 2 Microbiota in the gut - ©DSGiP

Human microbial colonization begins at birth. Infants born vaginally are initially colonized with microbial colonies that have a maternal signature, while those delivered by caesarean section harbour colonies that more closely resemble the skin microbiota. The Microbiota then diversifies over the first few weeks of life to form a complex,

[3] in vivo: in living organisms

anaerobe[4]-dominated microbial community. At the same time, the hypothalamic–pituitary–adrenal (HPA) axis becomes activated, which has an impact on the enteric nervous system (ENS) that innervates the gastrointestinal tract (GIT). Finally, the human gut microbiota rapidly expands and reaches an adult-like stage by three years of age.

The composition of the microbiota is altered throughout the lifespan and is dependent on dietary habits, stress, xenobiotics (antibiotics and pesticides), exercise, circadian rhythm (sleep/wake rhythm) and disease state.

Function and actions

The microbiota has long been known to play a relevant role in the health of the host. The gut bacteria help break down certain nutrients, which can then be metabolized by host cells. They can also produce substances which play a significant role in the brain as neurotransmitters, or as neurotransmitter precursors (GABA, tryptophan, serotonin, histamine, dopamine). These neuroactive products can target the CNS via the bloodstream and can also influence neurons in the ENS.

A healthy gastrointestinal tract, in the homeostatic state, has a stable commensal microbiota that play a relevant role in the health of the host:

- Provides nutrition and energy (including production of vitamins)
- Helps to keep the integrity of the intestinal epithelial barrier
- Helps in the integrity of metabolic and immune systems
- Helps to resist to pathogens
- Produces (or acts in the production) of neurotransmitters (GABA, dopamine, histamine, tryptophan…)
- and play a role in the gut-brain-axis

The Gut-Brain-Axis

The brain-gut axis reflects the bidirectional[5], constant communication between the central nervous system (CNS) and the gastrointestinal tract. There is also a growing body of evidence that the intestinal microbiota influences the brain-gut interactions in

[4] Microorganisms that don’t need molecular oxygen for their metabolism.

[5] in both directions working

different points of time (from early life to neurodegeneration), so the term microbiota-gut-brain axis has been proposed.

The communication between gut and brain occurs via:

- Vagus nerve – directly connects the gut to the brain and sends signals in both directions. It plays a special role in stress response

- Neurotransmitters – chemical substances act as messengers carrying information from one neuron to another. They can alter CNS functions and influence emotions. Many of these neurotransmitters are also produced by your gut cells and microbiota. A large proportion of serotonin, for instance, is produced in the gut.

- Short-chain fatty acids (SCFA) – our microbiota is able to produce chemicals that affect how the brain works. SCFA, such as butyrate, propionate and acetate are important to control food intake, to the integrity of blood-brain-barrier and to control stress. In addition, they form an alternative fuel for all cells, especially brain cells.

- Immune response – gut and brain are also connected through the immune system. Gut immune response or inflammation can lead to gut leakage and systemic inflammatory response as well as brain disorders.

Through all these pathways, gut microbiota exerts a widespread influence on key neurological and behavioural processes and seem to be especially relevant at the beginning and at the end of human life course. Early-life gut microbiota may play a role in shaping neuronal networks and influencing cognitive, emotional and social domains. Aging is associated with alterations in intestinal microbiota composition, structure and function, which plays an important role in the development of neurodegenerative diseases.

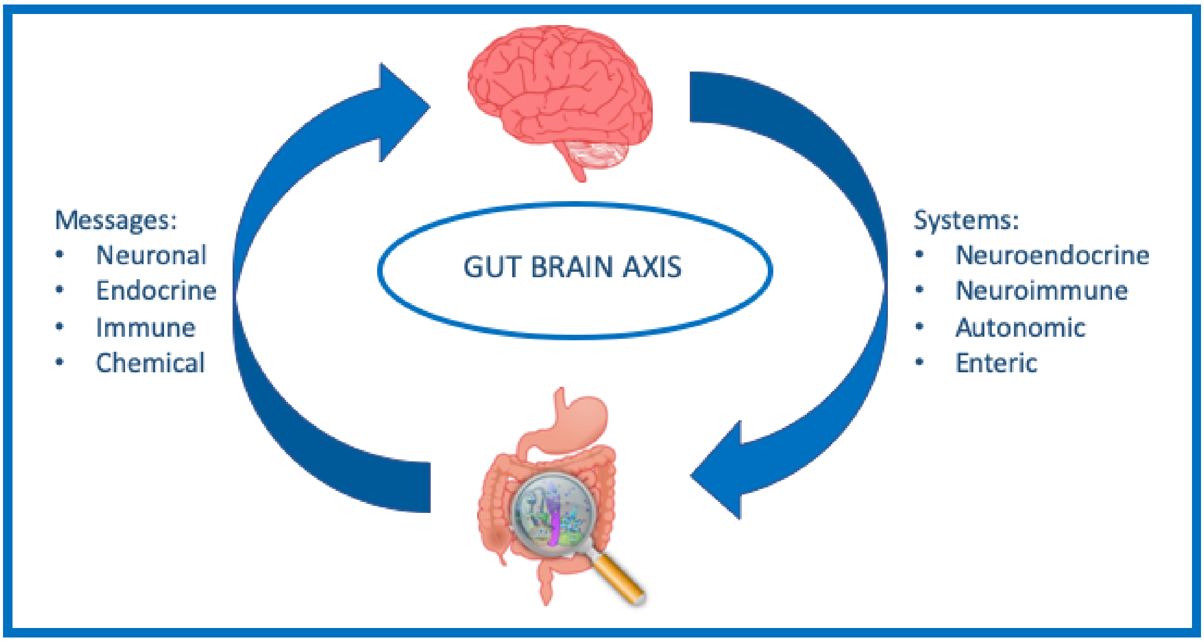


Figure 3 The Gut-Brain-Axis - ©DSGiP

Gut microbiome and Alzheimer's disease

In AD patients, a clear decreased microbial richness and diversity is observed. They also present a distinct composition in gut microbiota compared to asymptomatic age- and sex-matched individuals. It has been proposed that these broad-scale changes (dysbiosis) may play important roles in disease progression, potentially through immune activation and systemic inflammation.

Some remarkable features of the microbiome of AD patients were reported in experimental and clinical studies:

1. Low abundance of Firmicutes and *Bifidobacterium* and increased Bacteroidetes
2. Increase abundance of pro-inflammatory *Escherichia/Shigella* taxon and reduction in anti-inflammatory *E. rectale*.
3. An increase *in Rikenellaceae* and a decrease in Akkermansia.

Interestingly, reduced levels of Akkermansia characterize gut microbiota of mice with obesity and type 2 diabetes, two potentially modifiable risk factors for AD.

Neuroinflammation is a key feature in the physiopathology of AD. An inflammatory trigger can lead to microglia activation and neuroinflammation. In a chronic inflammation scenario, a self-perpetuating cycle of inflammation takes place and the result is diffuse amyloid deposits and neurodegeneration. Please refer to the Causes[6] section on the KsD website to learn more.

In humans, intestinal permeability increases with age, leading to hyperstimulation of the immune system, elevations in peripheral pro-inflammatory cytokines and a constant state of low-grade inflammation, also known as "**inflamm-aging"**.

Alterations in gut microbiota composition together with the increase in intestinal permeability observed with age lead to the translocation of microbes or microbial components (like lipopolysaccharide -LPS) from the gut and induce systemic and CNS inflammation.

While the study of the gut-brain axis in AD is still in its infancy, promising preclinical and clinical data suggest that the modulation of gut microbiota through dietary ingredients or probiotics may provide a means to counteract the development or progression of neurodegenerative disease (you can find a list with clinical trials at Alzheimer's Research section[7]).

The role of gut microbiota in the development of AD:

1. Lipopolysaccharides[8]: The major outer membrane component of gram-negative bacteria is lipopolysaccharide (LPS). I*n vitro* and *in vivo* studies have shown that LPS promotes microglia activation, inflammation and amyloid deposition. Recently, LPS presence has been detected in the hippocampus from AD patients. The plasma concentration of LPS in AD patients is also significantly higher than in healthy people.
2. Bacterial Amyloids: The gut microbiota is a source of amyloids. The production of amyloid proteins helps bacterial cells to bind to each other forming biofilms and to resist destruction by physical or immune factors. The exposure to bacterial amyloid proteins in the gut may cause awareness of the immune system, which will respond strongly when in contact to endogenous[9] production of neuronal amyloid in the brain.
3. Gut barrier dysfunction: Gut inflammation and dysbiosis is directly associated with gut barrier dysfunction. Increased intestinal permeability ("leaky gut")

[6] https://kompetenz-statt-demenz.de/en/was-ist-demenz/causes/

[7] https://kompetenz-statt-demenz.de/en/was-ist-demenz/alzheimers-research/

[8] LPS are relatively heat-insensitive compounds consisting of fat-like (lipo) and sugar components (polysaccharides). When the bacteria decompose, parts of them are released and have a toxic effect. These parts are called endotoxins and are not released by intact bacteria.

[9] produced in the body

causes migration of bacteria to neighbouring tissues (bacteria translocation) and discharge of harmful substances into the bloodstream. Some probiotic strains such as *Lactobacillus* and *Bifidobacterium*, enhance intestinal barrier, increasing expression of proteins forming tight junctions (the connection between your intestinal cells). The abundance of mucin-degrading bacteria *Akkermansia muciniphila* also improves the gut barrier function. On the other hand, different pathogenic bacteria can produce exotoxins which mediate changes in tight junctions, disrupts adherence of gut cells and increases intestinal permeability.

Conclusion:

A well-composed microbiota (intestinal flora) plays an essential role for our health, as it is directly connected to the nervous system via the gut-brain axis and thus plays an important role in essential neurological processes. If the microbiota is not balanced, i.e. the composition shifts in favour of the 'bad' germs, this can contribute to chronic inflammation and disruption of physiological barriers, which can have devastating consequences for nervous tissue, including neurodegeneration and dementia.

But the good news is that, with this knowledge, we have an effective therapy option through a targeted change in the composition of the microbiota and thus a further weapon in the fight against Alzheimer's disease.

What can I already do by myself?

The key to successful prevention of Alzheimer's disease and many other dementia-related diseases lies in a diet that is aimed at keeping the intestinal flora healthy and in reducing permanent mental stress. You can escape the permanent stress through creative artistic activities or mental techniques such as breathing exercises, yoga or meditation. Concerning nutrition, there are very simple measures to ensure optimal protection against neurodegenerative diseases. Some important ones are listed below.

12 Specific measures regarding nutrition that you can implement immediately

1. **Avoid industrially processed food as far as possible, especially junk food, and concentrate on whole foods from organic farming whenever possible**
2. **Consider diversity in nutrition as a guiding principle; alkaline foods should be preferred**
3. **Regular consumption of probiotics: Yoghurt with active cultures, kefir, sour milk and fermented foods (so-called postbiotics) such as sauerkraut, kimchi, miso, Taipei)**
4. **Sugar reduction, in particular with regard to refined sugars and/or fructose in foods and beverages (processed products) ,as far as possible**
5. **Fasting in different ways**
6. **Avoid wheat and wheat products**
7. **Alcohol only in moderation**
8. **Higher consumption of foods with prebiotic effects (= high fibre content): crushed linseed, flea seed husks, red berries, chicory, artichokes, asparagus, root vegetables, onions, leeks, garlic, broccoli**
9. **Consumption of foods containing resistant starch (green bananas, sweet potatoes, previously cooled potatoes, rice, etc.)**
10. **Enjoy vegetable juices and green smoothies**
11. **Avoid acid inhibiting drugs (e.g. proton pump inhibitors) and replace them with natural treatment methods**
12. **avoid antibiotics as far as possible (therefore also use animal food, if possible exclusively from organic or pasture farming in order to minimise antibiotic uptake from these sources); if antibiotic therapy is required, it is recommended to take probiotics in parallel (but at different times of the day) and continuously.**

Further information

Links

Knowledge stops Dementia website: https://kompetenz-statt-demenz.de/en/
Registration KsD-Newsletter: https://kompetenz-statt-demenz.de/en/newsfeed/subscribe/

Here you can find an interesting video about the microbiome and the gut-brain axis: **How bacteria rule your body - The Microbiome** (English with German subtitles)

https://youtu.be/VzPD009qTN4

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