Gut–brain communication

The gut–brain axis is an emerging field of research that explores how trillions of microbes living in the gut can influence the brain and overall health. Science writer Jessica McKendrick explores how current research is implicating microbes in shaping mood, memory and the risk of disease

Jessica McKendrick

The human body is home to trillions of microbes. Most inhabit the gut, forming a thriving, bustling ecosystem called the gut microbiome. The large and small intestine are populated by thousands of different species of bacteria, viruses, fungi and protists. Each interact with many body systems assisting with biological functions. Over the past decade, scientists have investigated how these microbes in the intestine may influence mood, stress, memory and even neurological disease through controlled interactions with the brain, introducing the concept of the gut–brain axis.

The gut–brain axis is a communication network between the central nervous system and the **enteric nervous system**: a network of neurones within the wall of the digestive tract, controlling its function. It involves both direct (neurones) and indirect (endocrine and immune system) pathways that link the brain's cognitive and emotional response to how the intestines work. The axis is bidirectional, meaning that the gut can influence the function of the brain (see Figure 1). Central to this communication system is the gut microbiome (see Box 1).

How microbes influence the brain

At first glance, it may seem unlikely that gut microbes could affect the brain. The blood–brain barrier works effectively to prevent potentially harmful substances from entering the central nervous system. However, researchers have identified several pathways detailing how microbes in the gut can communicate with the brain, working to maintain homeostasis.

Afferent sensory neurones in the vagus nerve carry feedback from gut to the brainstem, which then communicates with the hypothalamus and the limbic system, areas of the brain involved in controlling emotions. Both the hypothalamus and the limbic system can send signals back to the gut. Notably, when a person is stressed, the limbic system activates **efferent neurones** that influence the autonomic nervous system, controlling digestion without conscious effort. This means that stress can directly affect how the gut works.

Many bacteria, including *Lactobacillus* and *Bifidobacterium*, live in the gut and produce the neurotransmitter gamma-aminobutyric acid. Other bacteria, such as *Enterococcus* and *Escherichia*, produce the neurotransmitter serotonin, while some *Bacillus* species have been shown to produce dopamine. Bacteria also produce short-chain fatty acids, such as butyric acid and propionic acid. These acids can activate

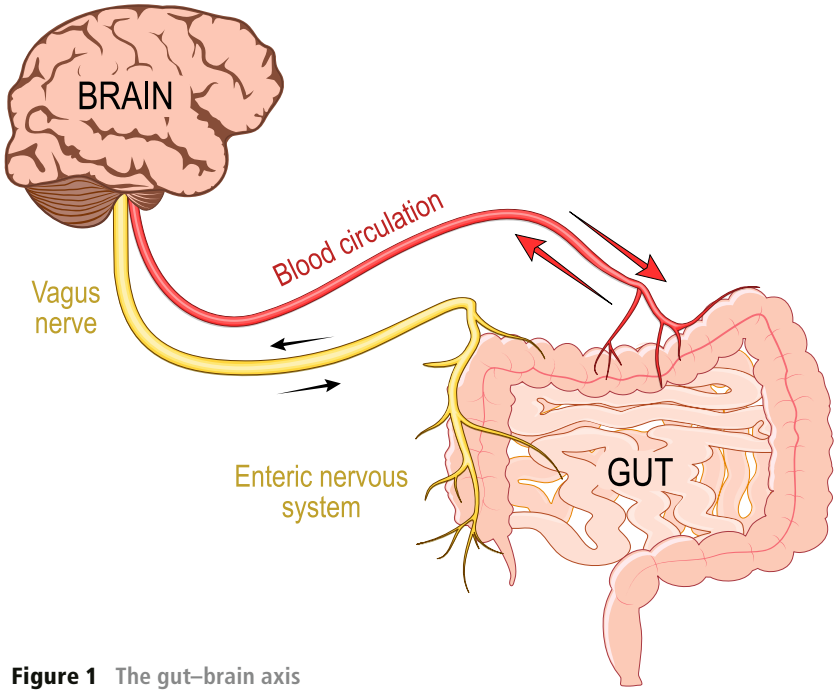

Figure 1 The gut–brain axis

Box 1 Establishing the gut microbiome

Development of the gut microbiome begins at birth. Colonisation begins when a fetus is in the uterus, and is established after birth, continuing to mature during early childhood. Newborn babies delivered vaginally acquire microbes from their mother's vaginal microbiome, while infants delivered by caesarean acquire microbes from the mother's skin and the delivery environment.

Breast milk from the mother provides a unique variety of living microorganisms and milk oligosaccharides – complex carbohydrates that are not digested. These serve as prebiotics (probiotics and psychobiotics) that nourish beneficial gut bacteria.

The introduction of solid foods to the diet marks a significant transition in microbiome development. By the end of the first 3–5 years of life, a complex adult-like community of microbes has developed, which continues to adapt throughout life.

A complete gut microbiome hosts approximately 100 trillion microbes, representing as many as 5000 different species and weighing approximately 2 kilograms.

the **sympathetic nervous system**, which then triggers serotonin release from specialised sensory cells found in the gut. This serotonin affects the brain indirectly by stimulating the vagus nerve to influence mood and appetite.

Gut microbes constantly interact with the body's immune system. Dysbiosis refers to an imbalance in the microbiome, leading to a loss of beneficial microbes and an overgrowth of potentially harmful ones that can result in reduction in overall microbial diversity. Dysbiosis can activate immune cells in the gut and cause chronic inflammation, releasing inflammatory **cytokines** (see Figure 2). These activate sensory fibres of the vagus nerve in the gut wall, sending signals to the brainstem that then influence the emotional brain centres. This in turn can change brain activity and influence mood, linking the immune response with gut imbalance and mental health.

TERMS EXPLAINED

Afferent sensory neurone Nerve cell in the peripheral nervous system that transmits sensory information from receptors in the body towards the central nervous system (brain and spinal cord) for processing.

Cytokine Small signalling protein secreted by immune cells that acts as a messenger, regulating immunity, inflammation and blood cell production.

Efferent neurone Nerve cell that transmits signals away from the central nervous system to effectors, such as muscles and glands.

Enteric nervous system Part of the peripheral nervous system comprising millions of neurones embedded in the gastrointestinal tract wall.

Peripheral nervous system Part of the nervous system outside the brain and spinal cord connecting the central nervous system to the rest of the body.

Sympathetic nervous system A component of the autonomic nervous system that triggers the 'fight-or-flight' response, preparing the body for action, stress or danger.

The impact of stress

The gut microbiome also interacts endocrinologically with the hypothalamic–pituitary–adrenal (HPA) axis, the body's central stress response system. Changes in microbial composition can influence levels of cortisol and other stress hormones, while chronic stress can in turn disrupt the balance of the gut microbiome. When the body experiences stress, it activates the HPA axis, leading to the release of cortisol, a hormone that helps mobilise energy and supports short-term adaptation. In the short term, cortisol is beneficial. However, chronic stress results in

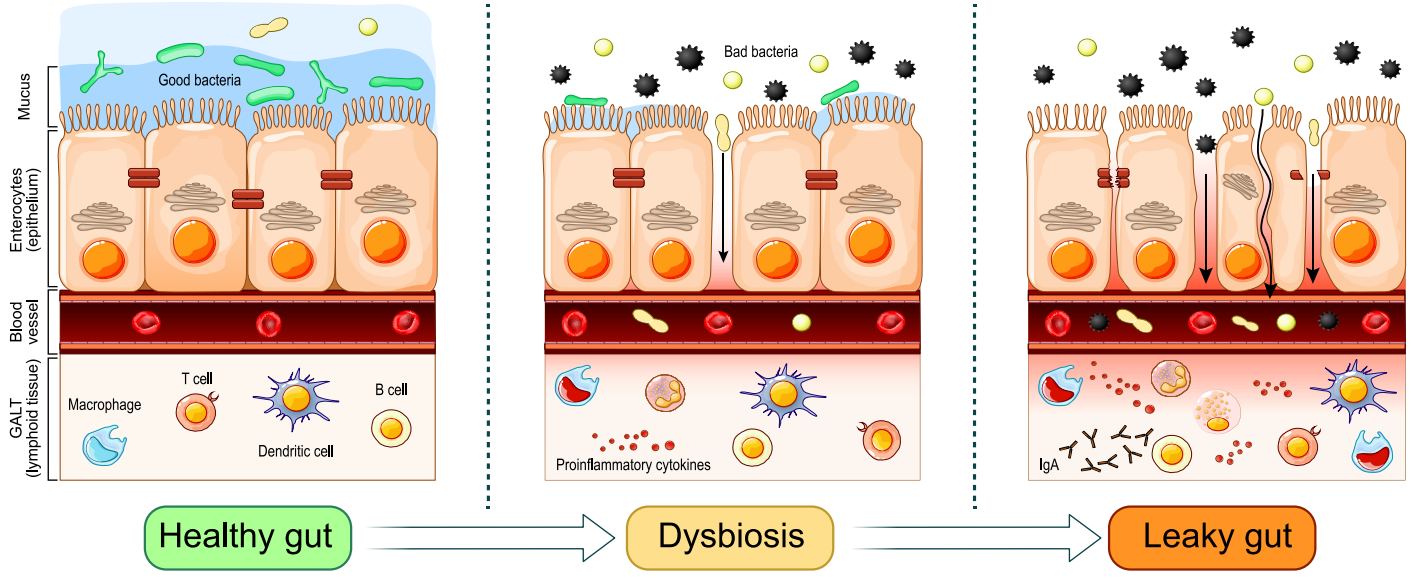

Figure 2 Dysbiosis and the leaky gut

persistently elevated cortisol levels, which can have harmful effects on both the gut and the brain.

Prolonged exposure to cortisol increases the permeability of the intestinal lining, allowing bacterial products to pass more easily into the bloodstream. This phenomenon, often referred to as 'leaky gut' (see Figure 2), triggers an immune response characterised by the release of inflammatory molecules such as interleukin-6 (IL-6). IL-6 can interfere with normal cortisol regulation, failing to switch off the stress response once passed. Such a disrupted feedback control results in a hyperactive HPA axis and sustained high levels of stress hormones. This results in a positive feedback loop in which stress promotes inflammation, inflammation impairs hormonal regulation, and hormonal dysregulation further amplifies stress.

Prolonged activation of this stress–inflammation pathway is associated with reduced serotonin levels in the brain's hippocampus, a region involved in mood regulation and memory. Such changes are consistently observed in anxiety- and depression-related disorders linked to chronic stress. Findings from germ-free mouse models further support the role of gut-mediated mechanisms in shaping stress responses. Figure 3 summarises the interactions.

Germ-free mouse studies

Much of what is currently known about the connections between the gut microbiome and the brain comes from animal research. Germ-free mice raised in sterile environments lack a gut microbiome, providing a powerful model for investigating how intestinal microbes influence physiological and neurological interactions. By comparing germ-free mice with conventionally raised mice with a typical gut microbiome, researchers have been able to identify striking differences across many biological systems.

In the absence of gut microbes, germ-free mice have impaired digestion and nutrient absorption, alongside disrupted antibody production and underdevelopment of the immune system. These findings highlight the essential role of the microbiome in supporting metabolic processes and immune maturation.

The effects of microbial absence also extend to the brain. Germ-free mice display altered brain morphology, decreased stem cell division, and increased permeability of the blood–brain barrier. Together these imply that gut microbes contribute to normal brain development and structural integrity. Indeed, these changes are accompanied by marked differences in behaviour. Compared with conventionally raised mice, germ-free animals have impaired learning and memory, reduced sociability and altered locomotor activity. This demonstrates that the presence of a healthy gut microbiome is closely linked not only to immune and metabolic function, but also to brain development and behaviour, strong evidence for the gut–brain axis as an integrated biological system.

Tailoring the gut microbiome

Given the abundance of research showing the significance of the gut microbiome to human health, there is much discussion about ways in which to diversify the gut microbiome as both preventative and curative measures to support various biological functions.

Diet

Diet remains the simplest way to shift microbiome composition. Research has found that high-fibre foods encourage the growth of short-chain fatty acid-producing bacteria, which support the integrity of the gut barrier to reduce inflammation. Diets rich in vegetables, fruit, legumes and wholegrains, like the Mediterranean diet, have been linked to improved moods. In contrast, diets high in sugars and saturated fats are known to reduce microbial diversity, instead increasing populations of pro-inflammatory microbes.

Probiotics

Probiotics are live microorganisms that, when consumed, can confer specific health benefits by influencing existing gut bacteria or producing

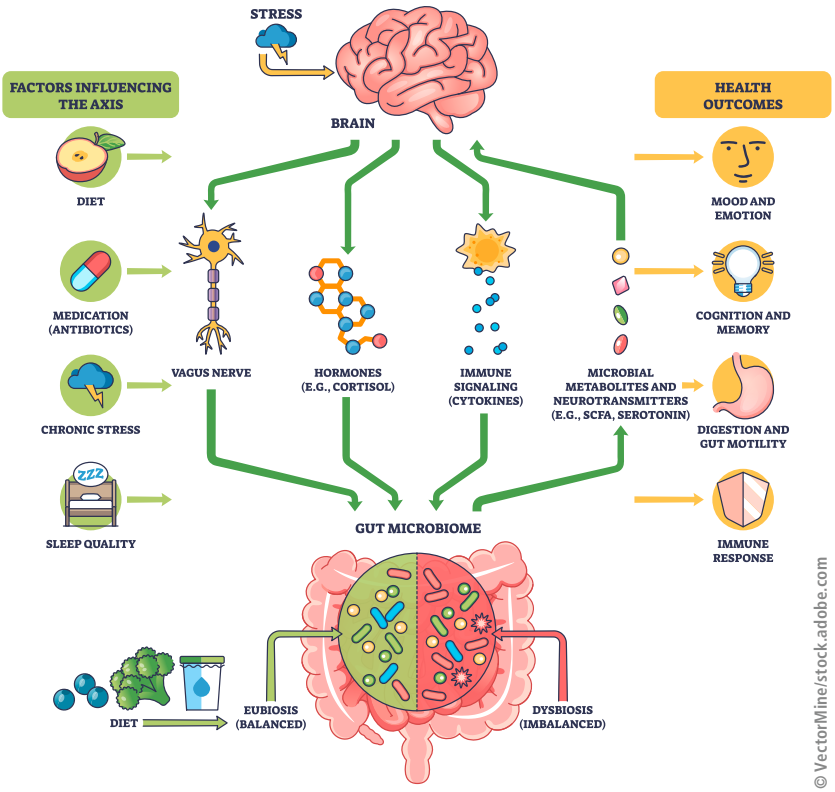

Figure 3 Influences on, interactions in and outcomes of the gut–brain axis

beneficial metabolites. Some probiotics, psychobiotics, appear to have particular effects on brain function and behaviour. Animal studies suggest that *Lactobacillus rhamnosus* can reduce anxiety by increasing the release of the inhibitory neurotransmitter GABA in the brain. Human trials with *Bifidobacterium longum* have reported reductions in stress and improvements in memory performance. These effects are thought to arise through a combination of mechanisms, including production of neurotransmitter precursors, interaction with the vagus nerve, and modulation of immune responses. However, probiotic effects vary widely between individuals, and commercially available probiotics are not yet regulated as medicines.

Stool transplantation

Faecal microbiota transplantation (FMT) – stool transplantation – involves the transfer of gut microbes from a healthy donor to a patient. The transfer involves either an oral capsule that remains intact until it reaches the colon, containing freeze-dried, live faecal microbiota, or an enema. Currently the procedure acts as a proven treatment for *Clostridioides difficile* bacterial infections, where normal gut bacteria have been disturbed following antibiotics. FMT is also proposed as a suitable treatment for ulcerative colitis, a chronic inflammatory bowel disease causing inflammation of the colon.

Further experimental work is investigating whether FMT can treat patients with depression or neurodegenerative disease. While FMT remains experimental and is not yet widely approved for neuropsychiatric conditions, early studies in specific populations, such as children with autism spectrum disorder, are exploring its potential effects on both gut and behavioural outcomes (see Box 2).

Box 2 Case study: autism spectrum disorder and faecal transplant

Many children with autism spectrum disorder (ASD) are reported to experience gastrointestinal problems, such as constipation, diarrhoea or abdominal pain, leading researchers to investigate the role of their gut microbiomes. Several studies report altered gut microbial composition in children with ASD, including reductions in beneficial *Bifidobacterium* species.

Preliminary studies are investigating the effect of faecal microbiota transplantation (FMT) in patients. The method involves transferring gut microbes from a healthy donor to a patient with ASD. Results from a small-scale trial showed that children treated with FMT showed improved digestive symptoms and some improvements in social behaviour and communication. Larger controlled trials are needed in order to make valid conclusions from these observations.

Further questions

The field of research surrounding the gut–brain axis is exciting, but leaves many questions unanswered:

- Which microbes are most significant for brain health?
- Can probiotics or diet reliably treat mental health disorders in the way medication can?
- How much of what we know about the gut microbiome and effects on the gut–brain axis is causation?

Finding answers to these questions is crucial for moving laboratory investigation into real-world therapeutics. What is known, however, is that the gut microbiome gathers recognition from many scientists as a 'super organ'. Recognised for its immense biological importance and potential, the gut microbiome serves as a strong reminder that sometimes it is the smallest organisms that can have the largest impact on health.

RESOURCES

Gut instincts – the secrets of your second brain:
https://tinyurl.com/gut-instincts-second-brain

Brain signals can change the gut microbiome in as little as 2 hours:
https://tinyurl.com/Brain-signals-gut-microbiome

2-minute neuroscience on the gut–brain axis:
https://tinyurl.com/2-minute-neuroscience

20 things you did not know about the gut–brain axis:
https://tinyurl.com/20-things-gut-brain-axis

Faecal microbiota transplantation:
https://tinyurl.com/faecal-transplant

KEY POINTS

- The gut microbiome develops during the first few years of life.
- There is a bidirectional signalling system between the brain and the gut.
- Disruption of the gut microbiome causes disease in mice and there is growing evidence of similar effects in humans.
- Future treatments may include faecal transplants.

Jessica McKendrick is an MSc science communications graduate from the University of Glasgow. With a BSc in human biology she focuses on using science writing and public engagement to make complex biomedical research accessible and impactful.