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# A Comprehensive Guide to the Gut-Brain Axis

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**Target audience:** For healthcare professionals interested in learning about the gut-brain axis.

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## Learning Outcomes:

**By the end of this article, you should understand:**

1. The role of the gut-brain axis
2. The factors that influence the gut-brain axis
3. The role of the gut-brain axis in health and disease

## What is the Gut-Brain Axis?

The gut-brain axis (GBA) is a bi-directional system of communication between the brain and the gastrointestinal tract. It links together the emotional and cognitive centres of the brain with peripheral control and function of the gut (1).

The vagus nerve is the primary mechanism of GBA communication, however, a complex network of other biochemical messengers also contribute to GBA communication. These parallel pathways involve neural, endocrine and humoral messengers (2, 3).

### Table 1: Components of the Gut-Brain Axis

| Component | Definition |
|---|---|
| The Central Nervous System (CNS) | The CNS comprises the brain and spinal cord. Within the brain, the hypothalamus acts as the centre of gut control (4). |
| The vagus nerve | The vagus nerve is part of the peripheral nervous system (PNS). It travels from the brainstem to the gut, with branches at the heart and lungs. It innervates the digestive system from the stomach to the transverse colon (5). Communication is bidirectional, although 90% of neurons are afferent (meaning that they send messages from the gut to the brain). |
| The Enteric Nervous System (ENS) | Sometimes referred to as the "second brain", the ENS is a branch of the autonomic nervous system found within the gut wall. It can control some actions of the gastrointestinal tract (GIT) independently, and receives messages from the GBA via neural and non-neural routes. |
| The Hypothalamic Pituitary Adrenal (HPA) axis | The HPA axis coordinates cortisol release in response to external environmental stressors. There are cortisol receptors in the gut wall. |
| Gut Associated Lymphoid Tissue (GALT) | GALT comprises more than 70% of total immune cells (6). It is involved in maturation and activation of the immune system and is an intermediary in the GBA (7). |
| The Gut Microbiome | The gut microbiome refers to a collection of living organisms within the gastrointestinal tract, comprising mainly bacteria (8). These bacteria communicate with the brain via a variety of pathways and are an important intermediary of immune/ inflammatory communication pathways. |

Due to advances in scientific research, the gut microbiome is now known to play an important role in influencing GBA communication. So much so that it is often referred to as the microbiota-gut-brain axis (7, 9). Much of the research in this area has been conducted in germ-free mice, which are bred in a sterile environment and therefore have no microbiome.

Mechanisms by which the gut microbiome communicates via the GBA includes (1, 2, 7):

- Modulating the intestinal barrier
- Stimulating vagal afferent sensory nerves
- Producing local neurotransmitters: gamma-aminobutyric acid (GABA), serotonin, histamine and acetylcholine
- Producing beneficial short-chain fatty acids (SCFA)
- Regulating the mucosal immune cells and antigen production

## What is the Role of the Gut-Brain Axis?

The role of the GBA is complex, multifaceted and at present, is not fully understood. However, research is ongoing and our understanding is rapidly evolving. It is widely accepted that the primary function of the GBA is to maintain gastrointestinal homeostasis and digestion (10), including peristalsis, pyloric and ileocolic sphincter control, secretion of gastric acid, bicarbonate and mucous, enzyme secretion and nutrient sensing (5, 6).

A simple and well-studied example of GBA communication is the cephalic stage of digestion, where upon the sight, smell, taste or anticipation of food, the brain innervates the GIT via the vagus nerve, to produce gastric acid (5, 6). Additionally, gut wall epithelial cells secrete peptides such as cholecystokinin (CCK), ghrelin and glucagon-like peptide-1 (GLP-1), which communicate with the brain to control satiety and hunger via the vagus nerve (7).

Stress is a well-known factor that can disrupt digestive functions. The GBA is very important for adaptive responses to environmental factors, including threats (7). The HPA axis stress response leads to slowing of gastric motility, acceleration of distal bowel motility, nausea and shifting of blood flow to the heart and lungs as part of the 'fight or flight' reflex (6).

The gut is known to have profound effects on mood, motivated behaviour, and cognitive function (7). More research is required in this area, especially in humans, however, GBA communication appears to be important in the regulation of emotional responses and resilience to stressors (7). One component of the GBA that may be important in this area is the neurotransmitter serotonin; 95% of which is made in the gut (7). Serotonin contributes to local gut motility and pain perception but also targets areas in the brain involved in mood regulation and cognition (1, 7).

## Factors Influencing the Gut-Brain Axis

Vast amounts of research into the GBA is being undertaken and thus, knowledge in this area is constantly evolving.

### Key Factors That Influence The Gut-Brain Axis

| Factor | Definition |
|---|---|
| Early Life Development | The ENS, also referred to as our 'gut-brain', begins to develop *in utero* (4). Laboratory-based studies on germ-free mice has shown that a lack of microbial colonisation negatively impacts nervous system development, neurotransmitter production, gastrointestinal function and stress response in animals (3). Emerging research in humans suggests that the early life microbiome is an important factor in later health outcomes and stress responses (7). |
| Stress and Trauma | Stress and trauma, especially during key early developmental stages can impact the development of neural communication pathways and the gut microbiome (7). In animal studies, chronic activation of the HPA axis due to stress leads to GBA pathway dysfunction (11).<br><br>In animal models, external psychological stress changes the composition (7) and total mass of the gut microbiome (2). In humans, studies are limited, but prenatal stress has been found to significantly impact the offspring's microflora, which has been related to reported changes in offspring GIT function (12). |

| | |
|---|---|
| Pathogens and Immune Activation | Gut parasite infections can impact brain function; for example, mice infected with *campylobacter jejuni* exhibit anxiety-like behaviour (13). Gut microbial balance appears to act as an important intermediary and contributes to regulation of the host inflammatory response (7), which alters signaling in the GBA (6). |
| Neurodegeneration/Injury | Studies using mouse models of brain injury show changes in the microbiome; this is thought to be mediated by altered GBA communication (3). |
| Dysbiosis | Dysbiosis may impact GBA communication by altering the production of microbe produced/mediated communication molecules. Conversely, dysregulation of the GBA can impact the physical environment of the gut microbiome, through changes in secretion of mucous and the biofilm layer where bacteria grow (2). Animal studies have shown that even short-term stress can significantly change microbiota composition and these changes can induce anxiety-like behaviour in mice (7). |

## The Gut-Brain Axis in Health and Disease

Interest in the role of the GBA in health and disease stems from an observation that many neurological disorders have gastrointestinal consequences, with high level of concurrence of psychiatric and gastrointestinal diseases.

### Irritable Bowel Syndrome

Irritable Bowel Syndrome (IBS), the most common functional gastrointestinal disorder, is often described as a disorder of the GBA, or more recently, the microbiome-gut-brain axis (2,4,7). IBS features disturbed gut motility and gut function alongside visceral sensitivity, increased pain sensation from the ENS (4) and altered communication with the CNS (14).

Stress and early life trauma are key risk factors in IBS (7). Furthermore, IBS is often comorbid with anxiety and depression (14). People with IBS have structural brain differences in the hypothalamus, including larger areas in the brain involved in pain processing compared with healthy controls (4,6). Brain structure within IBS sufferers is also linked to gut microbiome profile, indicating a role of the GBA (15).

Dysbiosis can occur post-GIT infection (4) and it is observed in people with IBS. Dysbiosis may lead to changes in the GBA serotonin metabolism, structural permeability and immune activation in the gut (4), which may contribute to visceral hypersensitivity and changes in gut motility.

Several therapies for the management of IBS symptoms target the GBA, such as Cognitive Behavioural Therapy (CBT), gut-directed hypnotherapy and use of probiotics (16). In addition, drugs traditionally used to treat depression, such as tricyclic antidepressants are sometimes used to manage IBS symptoms (17) through the modification of serotonin levels.

Modulation of the GBA and microbiome is a promising area of research in IBS. However, the 2016 British Dietetic Association guidelines for the dietary management of IBS (18) called for further high quality studies into the use of probiotics for IBS (19).

### Depression and Anxiety

People with depression have increased HPA axis responsiveness (7). Studies in mice show that early life stress (such as maternal separation) increases HPA activation, resulting in circulating stress hormones and changes in the microbiome, leading to depressive and anxiety-like behaviours (20). Interestingly, in germ-free mice these behaviours are not expressed, indicating a key role of the gut microbiome in mediating changes in mental health (20).

Different gut microbial profiles have been found in patients with depression versus healthy controls (7, 11). Animal studies have transplanted faecal microbiota from humans with anxiety and depression into germ-free mice, which led to adoption of some features of

these conditions (11). This may be related to the gut's role in the production of neurotransmitters such as serotonin (7). Interestingly, levels of tryptophan (the precursor of serotonin) are lower in depression (21).

Based on this proposed theory of GBA involvement, vagal nerve stimulation has been used as treatment of resistant depression (8). In the UK, NICE states that the benefits and risk of this treatment are uncertain (22).

## Obesity

Recent research has focused on the role of the microbiome-gut-brain axis in obesity. Dysregulation of the hedonic eating pathway (6, 8) and central appetite regulation (6) have been implicated as potential causes of obesity relating to the GBA.

Brain function imaging studies of people with obesity have shown enhanced expectation of reward to food cues, but less actual reward on eating these desired foods (6). This mismatch between expectation and actual reward derived from food may be mediated by GBA peptide communication.

The gut microbiota plays a key role in satiety signaling, and patterns of dysbiosis are seen in people with obesity (23). Faecal transplant from obese mice increases the energy harvested from diet and also body fat stores in germ-free mice (24).

More recently, bariatric surgery has become an area of interest due to its impact on the gut microbiome, which may, in part, be responsible for some of the metabolic (blood sugar control) changes and weight loss observed post-surgery (3, 23).

## Anorexia Nervosa

Studies in people with anorexia nervosa (AN) have found some differences in GBA signaling versus health controls, including increased HPA axis activation, high cortisol levels, low serotonin levels, inflammation and altered intestinal permeability (25). People with AN also have altered responses to satiety, hunger and hedonic reward signalling post food ingestion (6).

Again, dysbiosis is a feature of AN and it is associated with greater risk of anxiety and depression, changed SCFA production and GIT symptoms (25). However, it is not clear if the disease itself or malnutrition causes these changes.

## Neurological Disorders

Recent research has focused on the role of GBA communication (primarily immune activation and inflammation) on the progression of many neurological disorders (26,27).

### Parkinson's Disease

Parkinson Disease (PD) is a progressive neurodegenerative disorder which manifests primarily through symptoms of CNS deficit (28). Gastrointestinal symptoms, such as constipation, often coexist with or precede motor symptoms (26). The dopaminergic neurons which degenerate in PD are also found in the ENS, where they are responsible for GIT motility (29).

Vagotomy, a surgical procedure used to sever the vagus nerve, was historically used to reduce gastric secretions in the treatment of gastric ulcers. Some epidemiological studies have shown that following this procedure, patients were at a significantly lower risk of developing PD (30). However, these findings are not consistently reported in scientific literature (31). Research hypotheses have proposed that PD may originate in the ENS following changes in gut immune and microbial function before moving to the CNS following systemic inflammation (26).

Different gut microbial profiles have been found in patients with PD versus healthy controls (11). There has been research into the benefit of probiotic supplementation on PD progression, with some positive results in *in vitro* cell studies (32). A review of dietary management of PD symptoms (33) found that use of probiotics is promising in the management of constipation (although drug therapy is superior) and moderately beneficial in the management of symptoms such as abdominal pain and bloating.

### Alzheimer's Disease

Alzheimer's disease is also associated with an altered gut microbe profile (11). Amyloid plaques, the cause of neurodegenerative changes seen in AD, have precursor proteins expressed in the ENS which impact GIT motility, immunity and secretions (29). The evidence base for a role of the GBA is of low quality and more research is required (27).

### Autism

Autism spectrum disorder (ASD) also has high incidence of gastrointestinal symptoms (3,11) and can impact eating behaviour (11). Observational studies have found distinct gut microbial differences in people with ASD (11). Further studies are investigating the role of GIT immune activation in ASD (34).

## Summary

- In conclusion, the GBA is essential for bidirectional communication between the brain and the gut and it involves many methods of communication including neural, endocrine and humoral messages
- There are many factors which appear to influence the GBA including early life development, stress, immune response, neurodegeneration and dysbiosis. Disordered GBA may have a role in many conditions, including functional gut, psychiatric, neurological and eating disorders
- The majority of research on the GBA comes from animal studies and other preclinical models. Thus, caution is needed when interpreting the existing evidence base. Further high-quality, large scale human intervention studies are required across all clinical areas to advance our knowledge of the role of the GBA in health and disease

## Continuing Professional Development (CPD) Questions

**1) Which statement best describes the gut-brain axis:**

- a. A neural pathway by which the brain controls gut function.
- b. A bidirectional communication pathway involving neural and non-neural communication between the brain and the gut.
- c. A complex pathway in which the gut sends feedback to the brain via neural, hormonal and humoral messengers.

**2) The primary communication pathway between the gut and the brain is:**

- a. The vagus nerve
- b. The immune system
- c. The endocrine system

**3) Which of the following are not part of the gut-brain axis:**

- a. The gut microbiome
- b. The respiratory system
- c. The immune system

**4) The nervous system found within the gastrointestinal tract is called:uld:**

- a. The enteric nervous system
- b. The central nervous system
- c. The autonomic nervous system

**5) Dysbiosis and subsequent altered GBA communication is implicated in which of the following conditions:**

- a. IBS
- b. Obesity
- c. Depression
- d. All of the above

**6) Research into the role of the GBA in disease mainly consists of:**

- a. Epidemiology
- b. Human clinical trials
- c. Animal studies

Answers the on the last page

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## Answers

- 1. b
- 2. a
- 3. b
- 4. a
- 5. d
- 6. c

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