

The Quiet Conversation between Two Brains: Exploring Gut-Brain Axis: From Classical Unani

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Abstract: *The gut–brain axis (GBA) is a bidirectional communication system connecting the gastrointestinal tract and the brain through neural, neuroendocrine, immune and metabolic pathways. Modern research has highlighted the role of the enteric nervous system, vagus nerve, autonomic nervous system, enteroendocrine signalling, intestinal barrier and gut microbiota in this communication. The relationship between gastrointestinal function and the brain is also described in classical Unani literature. Ibn al-Quff, in Kitab al-Umda fi al-Jarajat, described neural relationships involving the gastrointestinal organs, while Ibn Rushd, in Kitab al-Kulliyat, discussed the influence of gastrointestinal disturbances on the brain in relation to Mizaj, Nafs-e-Dimagh and A'saab. Allama Kabeeruddin, in Al-Akseer, described the stomach as an organ capable of producing distress in the brain and discussed conditions such as Suda' and Sara'. Akbar Arzani, in Tibb-e-Akbar, also described headaches associated with gastric dysfunction, abnormal temperament and morbid matter. These classical descriptions provide a historical perspective on the relationship between gastrointestinal and neurological functions. Contemporary research has identified several mechanisms that may contribute to gut–brain communication, including vagal signalling, microbial metabolites, intestinal barrier function, immune activation and neuroendocrine pathways. Some of these mechanisms provide areas for comparison with observations described in classical Unani literature. However, concepts such as Bukharat, Akhlat, Sawda and Kaylūs should not be considered direct equivalents of modern microbial metabolites, immune mechanisms or neuroendocrine pathways. Instead, they can be examined as historical physiological concepts that may provide a basis for generating research questions. This review discusses the gut–brain relationship from both contemporary biomedical and classical Unani perspectives, while maintaining a distinction between historical descriptions and experimentally established mechanisms.*

Keywords: Gut–brain axis; Unani medicine; Mizaj; gut microbiota; vagus nerve; enteric nervous system; Bukharat; Akhlat; Suda'; Sara'; neurohumoral communication.

1. Introduction

The gastrointestinal tract and the brain maintain continuous two-way communication through a complex network involving neural, endocrine, immune and metabolic pathways. This integrated system is commonly referred to as the **gut–brain axis (GBA)**. It involves the central nervous system (CNS), enteric nervous system (ENS), autonomic nervous system (ANS), neuroendocrine pathways, immune mechanisms and the intestinal microbiota [1].

The GBA is not a single anatomical structure or pathway. Rather, it is a functional network through which information generated within the gastrointestinal tract can reach the brain, while signals originating from the brain can influence gastrointestinal motility, secretion, blood flow, appetite and other digestive functions [1,2]. The stomach and small intestine are highly innervated and also act as important sites for sensing nutrients and other changes within the gut. Vagal and splanchnic pathways provide major routes through which this information is transmitted to the CNS [3].

The modern understanding of the GBA has expanded with increasing recognition of the role of the gut microbiota. Microorganisms present in the intestine interact with the host through metabolic, immune, endocrine and neural mechanisms. Through these interactions, changes in the intestinal environment may influence processes beyond the digestive system, including stress responses, behaviour and brain function [4].

The relationship between the gastrointestinal tract and the brain is also described in classical Unani literature. Various Unani physicians described associations between gastrointestinal disturbances and neurological manifestations

through concepts such as *Mizaj*, *Akhlat*, *Nafs*, *A'saab*, *Bukharat* and disturbances of digestive function. These descriptions provide a historical framework for understanding how the gut and brain were viewed as functionally connected in Unani medicine.

Although these classical descriptions were developed within a different physiological framework from modern neurobiology, some of the observations can be discussed alongside contemporary concepts of gut–brain communication. However, such comparisons should be made carefully, as similarity in description does not necessarily indicate equivalence of mechanisms. The repeated descriptions of gastrointestinal influences on neurological functions in classical texts provide a useful basis for further comparative study between traditional Unani concepts and contemporary understanding of the gut–brain axis.

2. Modern Anatomical Basis of the Gut–Brain Axis

2.1 Enteric Nervous System

The enteric nervous system (ENS) is a highly organized network of neurons present within the wall of the gastrointestinal tract. It extends throughout the gastrointestinal tract and has an important role in regulating intestinal motility, secretion, local blood flow and different gastrointestinal reflexes [5,6]. Because of its extensive neuronal organization and a certain degree of functional independence, the ENS is considered the intrinsic nervous system of the gastrointestinal tract. It contains different types of neurotransmitters and signalling molecules, including acetylcholine, norepinephrine, adenosine triphosphate,

serotonin, dopamine, substance P, vasoactive intestinal peptide and somatostatin [37].

Although the ENS can regulate many gastrointestinal functions locally, it does not work completely independently. It communicates with the central nervous system through vagal and spinal pathways and helps in transmitting information related to nutrients and visceral conditions from the gut to the brain [5,6]. The ENS also interacts with enteroendocrine cells and gastrointestinal hormones. Enteric neurons possess receptors for different gut hormones and can participate in signalling through vagal and spinal afferent pathways [37,10]. Therefore, the ENS has a role both in the local regulation of gastrointestinal functions and in gut–brain communication.

Because of this extensive neuronal network and its ability to regulate several functions of the gastrointestinal tract with a degree of local independence, the ENS is commonly described as the “second brain” of the gut [5,37]. However, this term is used to describe its complex neuronal organization and functional autonomy; it does not mean that the ENS is anatomically or functionally identical to the brain.

2.2 Vagus Nerve

The vagus nerve is one of the main neural pathways connecting the gastrointestinal tract with the central nervous system (CNS). It carries sensory information from the gut to the brain and also provides parasympathetic efferent control of gastrointestinal functions [4,9]. The abdominal vagus contains a greater proportion of afferent fibres than efferent fibres, reflecting the importance of signals travelling from the gut towards the brain [7,38]. Through these sensory fibres, information about gastrointestinal distension, nutrients and other changes within the gut can be transmitted to the CNS [8,38].

Vagal fibres are also closely associated with enteroendocrine cells in the gastrointestinal tract. These cells respond to nutrients and other luminal stimuli and release gastrointestinal hormones such as ghrelin, cholecystokinin (CCK), glucagon-like peptide-1 (GLP-1) and peptide YY (PYY), which can influence vagal signalling [8,9]. In this way, information from the gut can reach the brain through both neural and hormone-related signalling. At the same time, vagal efferent signals from the brain can influence gastrointestinal functions. Thus, the vagus nerve acts as an important communication route in the bidirectional gut–brain axis [9-38].

2.3 Enteroendocrine Signalling

Enteroendocrine cells are specialized sensory cells present in the gastrointestinal tract. They respond to nutrients and other luminal stimuli and release different gastrointestinal hormones involved in digestion, appetite, metabolism and communication with the nervous system. Some enteroendocrine cells are closely associated with vagal afferent fibres, allowing information about the nutritional and physiological state of the gut to be transmitted to the CNS [9].

The communication is not limited to enteroendocrine cells and the vagus nerve. ENS neurons also express receptors for gastrointestinal hormones and can respond to hormonal signals within the gut. These neurons may further participate in signalling through vagal and spinal afferent pathways [10,11]. Therefore, enteroendocrine cells, the ENS and vagal pathways work together in transmitting information from the gastrointestinal tract to the brain.

2.4 Hypothalamic–Pituitary–Adrenal (HPA) Axis and Gut–Brain Relationship

The hypothalamic–pituitary–adrenal (HPA) axis is an important system involved in the body's response to stress and is closely related to gut–brain communication. During a stress response, the hypothalamus releases corticotropin-releasing hormone (CRH), which stimulates the pituitary gland to release adrenocorticotrophic hormone (ACTH). ACTH then acts on the adrenal glands and stimulates the release of cortisol. Cortisol helps the body respond to stress by regulating energy availability and influencing immune and gastrointestinal functions [12,39].

The relationship between the HPA axis and the gastrointestinal tract is bidirectional. Stress and repeated activation of the HPA axis can influence gastrointestinal motility, intestinal permeability, immune responses and the gut microbiota. At the same time, signals originating from the gut, including microbial, immune, hormonal and neural signals, can influence HPA axis activity and the stress response [12,39,40]. Thus, the HPA axis provides an important link between stress and changes occurring in the gastrointestinal system, while gut-derived signals can also contribute to the regulation of the stress response.

3. Major Pathways of Gut–Brain Communication

The GBA operates through several overlapping pathways.

3.1 Neural pathway

Neural communication involves the ENS, vagus nerve, spinal afferents and autonomic nervous system. Gastrointestinal sensory information is transmitted to the CNS, while autonomic efferent pathways allow the brain to regulate gastrointestinal function [4,7,8].

3.2 Neuroendocrine pathway

The hypothalamic–pituitary axis and autonomic nervous system participate in the regulation of gastrointestinal and stress-related functions. Gastrointestinal hormones can also influence appetite, energy balance and neural activity [12].

3.3 Immune pathway

The gastrointestinal tract contains extensive immune tissue and is continuously exposed to microbial products. Alterations in the microbiota or intestinal barrier may modify immune signalling and inflammatory pathways, which can subsequently influence the CNS [13].

3.4 Microbial and metabolic pathway

The gut microbiota produces and modifies biologically active compounds. These include metabolites and neuroactive substances capable of influencing host metabolism, immune responses and neural function [14–16].

4. Classical Unani Perspective on the Gut–Brain Relationship

The relationship between Digestive system and brain is discussed in detail in classical unani literature. These descriptions are explained different from modern physiology and at many places it explains manifestation of diseases of brain by disturbances in GIT tract.

4.1 Ibn al-Quff and the Neural Connection

Ibn al-Quff, in his work *Kitab al-Umda fi al-Jarajat*, described the relationship between the brain and gastrointestinal organs through nerves. His description refers to a cranial nerve rather than a spinal nerve and discusses its relationship with the gastro-oesophageal region. He also described a distinct neuronal arrangement within the layers of the gastrointestinal tract and recognized the contribution of spinal nerves to the innervation of abdominal organs[41].

4.2 Ibn Rushd and the Concept of Mizaj

Ibn Rushd, in *Kitab al-Kulliyat*, discussed the relationship between gastrointestinal disturbances and the brain through the concept of *Mizaj*. Disturbance of the temperament or physiological state of the gastro-oesophageal region was arising from several factors and involving different organs. The brain participates through *Nafs-e-Dimagh* and *A'saab*, and the pathology was also explained by involvement of concept of *Su-e-Mizaj* and *Su-e-Mizaj Maddi* [42].

5. Stomach as an Organ Influencing the Brain

Allama Kabeeruddin, in *Al-Akseer*, described several organs as capable of producing distress in the brain. Among these, the stomach was given particular importance, followed by the intestines, liver, spleen and diaphragm.

According to this description, gastric factors capable of producing distress to the brain include:

- 1) Abnormal hot temperament or excessive heat.
- 2) *Mirrah Saфра*.
- 3) *Imtala'-e-Meda*.
- 4) *Nafakh-e-Meda*.
- 5) *Khuloo'-e-Meda*.
- 6) *Zakawat-e-Hiss*.

These descriptions indicate that the stomach was considered capable of influencing cerebral symptoms through multiple functional and pathological conditions.

The importance of this observation becomes clearer when viewed alongside modern research, in which gastric distension, nutrient sensing, visceral afferent signalling, autonomic activity and gastrointestinal inflammation can influence central neural pathways [42]

6. Gastric Disorders and Headache in Classical Unani Medicine

Classical Unani literature provides several examples in which headache is associated with gastrointestinal disturbances.

One such example is **Suda'-e-Medi**, in which the stomach is considered to have a role in the production of headache. Another is **Suda'-e-Mevi'-e-Deedani**, in which intestinal disturbances, particularly those associated with intestinal worms, are described in relation to headache and other symptoms.

Allama Kabeeruddin, in *Al-Akseer*, described increased gastric sensation and increased *Quwwat-e-Medi* in association with *Suda'* and *Sara'*. The descriptions of *Suda'-e-Mevi'-e-Deedani* include headache, particularly in the frontal region, which may become more prominent during hunger or physical activity. Associated features described include unpleasant odour from the mouth or nose, with symptoms reportedly improving during rest or after the stomach becomes full.[42]

7. Akbar Arzani and Gastrointestinal Influences on Headache

Akbar Arzani, in *Tibb-e-Akbar*, described **Dard-e-Sar ba-Shirkat-e-Medi**, or headache associated with gastric involvement.

According to this description, headache may occur because of *Su-e-Mizaj* of the stomach, either alone or together with abnormal *Madda* or morbid humours. The resulting disturbance was considered capable of producing headache.

Arzani also described circumstances in which headache may occur when the stomach is empty, with an increase in internal heat, while in some cases headache may also be aggravated when the stomach is full [43].

8. Digestive Disturbance, Morbid Vapours and the Brain

Another example described in Unani literature is **Suda'-e-Khumari**, or intoxication-related headache. In this description, undigested alcohol is considered to undergo pathological transformation and generate morbid vapours, which subsequently ascend towards the brain and produce headache.

Within the classical Unani framework, the concept of *Bukharat* provided one explanation for how pathological effects originating within visceral organs could reach the brain.

From a contemporary perspective, alcohol is absorbed from the gastrointestinal tract and produces systemic and central nervous system effects through well-characterized pharmacological mechanisms [43].

9. Gut–Brain Relationship in Melancholia

Māḷankhūliyā, or melancholia, is another condition in classical Unani medicine in which digestive factors were considered important.

Certain digestive disturbances and dietary factors were associated with the formation of abnormal *Sawda*. The abnormal humour was described as capable of moving towards the brain and contributing to the development of melancholia [43].

10. Gastrointestinal Involvement in Sara'

The classical concept of **Sara' (epilepsy)** also includes descriptions of gastrointestinal involvement.

According to the Unani description, abnormal *Akhlat* of phlegmatic, melancholic or bilious nature- *Balghami*, *Sawdawi* or *Safrawi Akhlat*—may accumulate in the stomach and intestines. Their *Bukharat* were described as ascending towards the brain, where they were considered capable of producing constriction or obstruction and interfering with the pathways through which *Ruh* reaches the brain, ultimately contributing to the manifestation of *Sara* [43].

11. From Kaylūs and Bukharat to the Modern Gut–Brain Axis: A Conceptual Interpretation

The classical Unani description of gastrointestinal physiology includes processes involving digestion, transformation of material, formation of *Kaylūs*, *Akhlat* and, in pathological states, *Bukharat*.

Modern medicine shows that intestinal microorganisms participate in digestion and metabolism and produce numerous biologically active metabolites. These compounds may influence intestinal epithelial function, immune responses, endocrine signalling and neural pathways [14–16].

12. Gut Microbiota as a Modern Link Between Digestion and Brain Function

The intestinal microbiota interacts with the host through metabolites, immune pathways, endocrine signals and neural mechanisms. Certain microorganisms can influence the availability of neuroactive substances, including compounds involved in serotonergic, GABAergic and catecholaminergic signalling [14–16].

Short-chain fatty acids and other microbial products may also influence intestinal epithelial integrity, immune responses and systemic metabolism [34]. The gut microbiota can be considered one of the biological interfaces connecting gastrointestinal physiology with systemic and neurological functions.

13. Intestinal Barrier and Neuroimmune Signalling

The intestinal barrier protects the internal environment from excessive exposure to luminal microorganisms and their

products. Disturbance of barrier integrity may increase the systemic exposure to microbial components.

Lipopolysaccharide (LPS), a component of the outer membrane of Gram-negative bacteria, is one example of a microbial product capable of stimulating inflammatory responses. Increased exposure to microbial products may influence systemic immune signalling and, indirectly, neuroinflammatory processes [17].

The proposed sequence can therefore be summarized as:

Gut disturbance → altered microbial environment → intestinal barrier changes → microbial products/metabolites → immune and metabolic signalling → neural/endocrine effects → brain responses

This represents one of the major contemporary models through which gastrointestinal changes may influence brain physiology.

14. Gut–Brain Axis and Stress

Stress and the intestinal microbiota influence each other bidirectionally. Psychological and physiological stress can alter intestinal microbial composition and barrier function. Conversely, gastrointestinal disturbances and microbial changes may influence stress-related neural pathways [18].

Experimental studies have shown that intestinal infections can activate vagal afferents and central autonomic pathways. Infection with *Campylobacter jejuni*, for example, has been associated with activation of vagal and central autonomic pathways [19] and anxiety-like behavioural changes in experimental models [20].

Bacterial infection has also been associated with stress-related memory dysfunction in experimental animals [21].

15. Gut–Brain Axis and Neuropsychiatric Disorders

15.1 Autism Spectrum Disorder

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by difficulties in social communication and interaction together with restricted or repetitive patterns of behaviour.

Gastrointestinal disturbances and differences in gut microbial composition have been reported in some individuals with ASD. Studies have described changes in bacterial groups including *Clostridium*, *Sutterella*, *Prevotella*, *Coprococcus* and Veillonellaceae [22–25].

Experimental studies have further suggested that alterations in microbiota may influence behavioural and physiological abnormalities in neurodevelopmental models [26].

Nevertheless, these observations do not establish that gut microbiota alterations are an independent cause of ASD. The relationship is likely to be complex and influenced by multiple genetic, environmental, metabolic and neurological factors.

15.2 Obsessive–Compulsive Disorder

Emerging research has investigated the possible relationship between gut microbiota and obsessive–compulsive disorder (OCD). Alterations in microbial composition and microbial production of neuroactive compounds have been proposed as possible contributors to neuroimmune and neuroendocrine signalling [27,28].

15.3 Depression

Depression has been associated with changes in gut microbiota, intestinal permeability and immune signalling [14,29]. Microbial interactions with tryptophan metabolism may influence pathways involved in serotonin production, while other microbial products may affect GABAergic and related signalling systems.

Increased intestinal permeability may also facilitate exposure to microbial products such as LPS, potentially contributing to systemic inflammatory signalling in some patients [29].

15.4 Schizophrenia

Schizophrenia has also been investigated in relation to the gut microbiota, immune activation and intestinal barrier function. Alterations in several microbial populations have been reported in different studies [30–32].

16. Age, Diet and Other Factors Influencing the Gut–Brain Axis

The GBA is dynamic and is influenced by multiple factors. These include age, diet, metabolic status, genetics, geographical environment, antibiotic exposure and psychological stress [33].

Early-life microbial colonization is particularly important because the microbiota develops alongside the maturation of the immune and nervous systems. Experimental evidence suggests that alterations in early microbial exposure may influence anxiety-related behaviour and neurodevelopment [26].

Diet is another important determinant because dietary substrates influence microbial composition and the production of microbial metabolites. Consequently, dietary patterns may indirectly influence the gut–brain axis.

17. Integrating Classical Unani and Modern Perspectives

The classical Unani and modern descriptions of the gut–brain relationship comes from different schools of thoughts so it is important to describe both systems side by side rather than imposing on each other.

The central point of comparison is classical Unani physicians described modern microbiology or neurophysiology in different terms. They recognized a **functional relationship between the digestive system and the brain**, including the

possibility that disturbances in the stomach and intestines could produce cerebral manifestations.

Modern research provides biological mechanisms that can explain several types of gut-to-brain communication, particularly through neural, endocrine, immune and microbial pathways.

18. Discussion

The modern concept of the GBA has established that gastrointestinal physiology is closely linked with brain function. The ENS, Vagus nerve, Autonomic nervous system, Enteroendocrine cells, Immune system and gut microbiota form an interconnected network through which information can move in both directions [1–4].

The classical Unani literature provides a different perspective on this relationship. Descriptions by Ibn al-Quff, Ibn Rushd, Allama Kabeeruddin and Akbar Arzani repeatedly associate gastrointestinal disturbances with neurological manifestations. Headache, *Sara'*, melancholia and other cerebral symptoms were discussed in relation to gastric or intestinal abnormalities.

Particularly importance is assigned to the stomach. Classical descriptions explain altered gastric temperament, fullness, distension, abnormal digestive processes and other gastric disturbances as potential causes of cerebral symptoms. Modern physiology also demonstrates that the stomach and small intestine are highly innervated and are important sites of nutrient and visceral sensing [3,4].

The modern discovery of gut microbiota provides more information. Microorganisms participate in metabolism, production of biologically active compounds, immune regulation and intestinal barrier maintenance [14–16]. These mechanisms provide plausible biological pathways through which gastrointestinal changes may influence the brain.

However, a direct relationship between classical Unani concepts and modern physiologies and concepts are scientifically inappropriate. For example, *Bukharat* are not microbial metabolites, and *Sawda* is not a particular neurotransmitter or inflammatory mediator. Such Correlation are only applicable on terms of Conceptual understanding.

Classical recognition of digestive involvement in neurological disorders can be examined through modern research into microbiota, intestinal permeability, neuroimmune signalling and metabolic pathways.

19. Conclusion

The gut–brain axis represents a complex bidirectional communication system involving neural, endocrine, immune and microbial pathways. Modern research has established important roles for the enteric nervous system, vagus nerve, autonomic nervous system, enteroendocrine cells, intestinal barrier and gut microbiota in maintaining communication between the gastrointestinal tract and brain.

Classical Unani physicians also described relationships between gastrointestinal disturbances and neurological manifestations. Ibn al-Quff discussed neural relationships involving the gastrointestinal organs, while Ibn Rushd described gastrointestinal disturbances in relation to *Mizaj*, *Nafs-e-Dimagh* and *A'saab*. Allama Kabeeruddin and Akbar Arzani described several forms of headache and other neurological manifestations in association with gastric and intestinal disturbances. Classical descriptions of *Mālanikhūliyā* and *Sara'* further demonstrate the importance given to digestive factors in neurological disorders.

These descriptions are not directly correlated to modern vagal signalling, microbial metabolites, neurotransmitters or neuroimmune mechanisms. but they provide an important conceptual recognition that the physiological condition of the digestive system may influence the brain.

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