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GUEST EDITORIAL:

Gut–Brain Axis and Gut–Mind Interaction: Clinical, Psychosomatic, and Public Health Perspectives from Pakistan

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ABSTRACT
The gut-brain axis is a two-way transmission system between the gastrointestinal tract and the central nervous system via neural, hormonal, immunological and microbial pathways. Accumulating evidence is showing that gastrointestinal physiology has a strong impact on mood, thinking, and behaviour while psychological stress can have a strong impact on gut motility, secretion, permeability, immune activation and microbiota composition. Functional gastrointestinal disorders, in particular, irritable bowel syndrome, and functional dyspepsia are the best established clinical models for this interaction. Data from Pakistan, but not abundant, seem to persistently show a high prevalence of functional gut pathology with significant psychiatric co-morbidity (particularly anxiety and depression). Emerging local evidence has also mostly suggested associations between gut health and cognitive performance. This brief review in the discussion highlights role of biological mechanisms, clinical presentation, regional epidemiology and public health implications of gut - mind interactions with special reference to Pakistan.

KEYWORDS
Gut brain axis, Microbiota, Irritable bowel syndrome, Functional gastrointestinal disorders, Anxiety, Depression, Pakistan.

INTROCUCTION

The interaction between the gastrointestinal tract and the central nervous system has become one of the most dynamic and clinically relevant fields of the modern medicine and psychiatry[1]. Previously considered to be relatively independent systems, the gut and the brain are now known to be part of an integrated system of communication dubbed the gut-brain axis[1,2]. This paradigm shift has profound implications to understand the pathophysiology of a number of gastrointestinal, psychiatric and psychosomatic disorders. A bidirectional gut-brain axis is possible via neural, endocrine, immune and microbial pathways[1]. Psychological stress, emotional disturbance, and psychiatric illness can have a detrimental effect on gastrointestinal function, while chronic disorders of the gut can have an inverse effect on mental health, cognitive function and general quality of life. These interactions have particular relevance in low and middle-income countries like Pakistan, where the levels of high psychosocial stress, rapid urbanization as well as inadequate integration of mental health care is prevalent. Functional gastrointestinal disorders are an example of the gut-brain connection, as patients have significant GI symptoms without any underlying structural dysfunctions[4]. An understanding of the biological foundation and clinical implications of gut-brain interaction is a necessary prerequisite for the development of integrated forms of healthcare-to help address the physical and psychological responses to illness.

Biological Basis of the Gut–Brain Axis

The gut-brain axis is mediated through a complex and highly integrated network mediated by a combination of the enteric nervous system, the autonomic nervous system, the vagus nerve, neuroendocrine, immune mediator and gut microbiota[1,5]. The enteric nervous system has a vast network of nerve cells

that is able to regulate gastrointestinal function independently and in constant communication with the central nervous system.

Neural communication through the vagus nerve is at the core of the transmission of sensory information from the gut to areas of the brain involved in emotions, stress and cognition[5,6]. Altered Vagus nerve signaling has been implicated in the cause of functional gastrointestinal disorders as well as mood disorders. The neuroimaging data is also clear showing an abnormal activation of regions of the brain associated with pain perception, emotional control, and executive function in patients with functional gastrointestinal disorders.[6] Endocrine pathways are another important component to the gut-brain communication. The GI tract is the largest endocrine gland in the body, and secretes hormones such as serotonin, peptide YY, glucagon- like peptide-[2], and cholecystokinin that have an influence on appetite, mood, stress reactions, and GI motility[2,6]. Approximately ninety percent of all the serotonin in the body is produced in the gut, thus stressing the importance of the gut in emotional and behavioral dysregulation.

Immune-mediated signaling is the other way in which the gut and brain are connected. The gut-associated lymphoid tissue is a major immunological organ and cytokines released during the immune activation process can affect central nervous system function[3,7]. Chronic low-grade inflammation has been suggested to be an overarching pathophysiological mechanism in functional gastrointestinal disorders, depression, and anxiety.

The gut microbiota has emerged as a major player in determining communication that occurs between the gut and brain. Trillions of microorganisms that live in the gastrointestinal tract produce short-chain fatty acids, neurotransmitters, and neuroactive metabolites that affect gut permeability, immune reactions, and neural communication[2,3]. Dysbiosis has been repeatedly linked to anxiety, depression symptoms and cognitive impairment[7].

Clinical Manifestations of Gut–Mind Interaction

Functional gastrointestinal disorders are the most obvious clinical signs of gut - mind interaction[4]. Among these disorders, irritable bowel syndrome is the most extensively studied and a prototypical condition to understand gut-brain dysregulation. Irritable (or Intermittent) Bowel Syndrome is the name given to abdominal pain accompanied by bloating and diarrhea or constipation that recurs without any other obvious structural pathology causing the problem [4.] Psychiatric comorbidity is common with anxiety and depressive disorders in approximately forty to sixty percent of the patients[4,8]. Psychological stress, early life adversity, dysfunctional coping mechanisms and changes in gut microbiota composition all play a role in the severity and/or duration of symptoms.

Functional dyspepsia is another common functional gastrointestinal disorder that is highly associated with the psychosomatic state of mind.[9] Patients often report symptoms of anxiety, depression, and somatisation, which have a significant impact on the perception, use of healthcare, and quality of life. Similar gut-mind interaction has been described in functional constipation, functional abdominal pain syndromes, etc.
Beyond the application of functional gastrointestinal disorders, there is also emerging evidence on how changes in gut flora are potentially involved in disease aetiologies for primary psychiatric disorders such as major depressive disorder and anxiety disorders[7]. Although causality in these processes is still being examined, these findings support the theory of two-way interaction between gut health and mental health.

Evidence from Pakistan

Although population-based research on the topic is scarce, provided evidence from Pakistan shows a consistent relationship

between functional gastrointestinal diseases and psychological distress. Recent studies on medical students and young adults have reported the prevalence of irritable bowel syndrome between twenty and thirty-four percent, which is significantly higher than reported prevalence in many Western populations[8].

Hospital-based studies from Pakistan help to drive home the extent of psychiatric comorbidity. Anxiety has been reported in up to seventy percent and depression in approximately fifty percent of patients with irritable bowel syndrome, much more than patients seen in the healthy control groups [8, 9]. These findings point to the importance of routine assessment for psychologic issues in gastrointestinal practice.
Emerging Regional Evidence Also associations with indices of gut health and cognitive performance, specifically memory, attention and processing speed, have also been indicated in emerging regional evidence[10]. Although preliminary, these are data that suggest that gut--brain interactions may be more widespread than in the emotions area and may cross into cognitive domains.

Sociocultural factors such as dietary patterns, chronic psychocrine stress, stigma against mental disease, lack of access to an integrated healthcare facility possibly worsen the Gut-Mind disorders in Pakistan. Patients frequently come to the doctor's office with somatic gastrointestinal symptoms with concomitant, under-recognized, and untreated psychological distress.

Clinical and Public Health Implications
Although population-based studies are scarce, other studies conducted in Pakistan have all shown a strong link between functional gastrointestinal disorders and psychological distress. Recent studies in medical students and young adults show irritable bowel syndrome prevalence between twenty to thirty-four percent, a significantly higher prevalence than many Western populations reported in the literature.[7,8] Hospital-based studies from Pakistan report the extent of psychiatric co-morbidity further. Anxiety has been reported in up to seventy percent and depression in about fifty percent of patients with irritable bowel syndrome, and these rates are much higher than the levels found in healthy controls [8,9]. These findings highlight the importance of routine use of psychological assessment in gastrointestinal practice. There is also emerging regional evidence of links between measures of gut health and cognitive functioning, especially memory, attention, and processing speed.[10] Although preliminary, these data suggest that the gut-brain interactions may go beyond the control of emotion to the cognitive domains.

Sociocultural factors such as dietary patterns, chronic psychosocial stress, stigma associated with mental illness problems, and poor access to these integrated healthcare services may add to the onset of the gut-- mind disorders in Pakistan. Often patients present with somatic gastrointestinal complaints in the face of underlying psychological distress that is under-recognized and treated.

Limitations and Future Directions
Current evidence from the region of Pakistan is constrained by small sample sizes, cross-sectional study designs and lack of the standardized diagnostic tools. Population-based surveys and longitudinal studies, as well as microbiome profiling in various groups of individuals, are needed to better describe the gut--mind interactions. Controlled intervention trials of integrated treatment models should receive the highest priority.

CONCLUSION
The axis between the gut and the brain is one of the most basic connections between the gut and mental health. Evidence from Pakistan is similar to that from other global studies showing a high prevalence of functional gastrointestinal disorders and robust associations with anxiety and depression. Understanding gut-mind interaction is key to

effective, integrated and patient-centered models of healthcare, especially in resource-limited settings of high stress. Strengthening local capacity in research and interdisciplinary work in policymaking and practice will be part of tackling this increasing burden of health.

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