The gut-brain connection

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GUT-BRAIN
CONNECTION

gut-brain axis (GBA)

- Patients who have gastrointestinal disorders also have high psychiatric comorbidity.
- the gastrointestinal tract and the brain are intimately connected through bidirectional neural, endocrine, and immune pathways. Collectively, these pathways are referred to as the gut-brain axis (GBA).
- This complex communication system ensures the homeostasis of the gastrointestinal tract and influences the motivation for processing higher cognitive functions.

- THE CLOSE RELATIONSHIP between the gut and the psyche means that there are many examples of biopsychosocial relationships in the patient population seen by gastroenterologists.

- Life stressors and mood disorders are thought to play a large part in the symptoms, presentation, and course of the disorders.

- The most prominent disadvantage of the functional and organic terminology is the reinforcement of dualistic thinking—the separation of mind and body.
- For convenience, the term functional gastrointestinal disorder will be used i. However, a multifactorial view of illness should be maintained
- should bear in mind the frequent comorbidity of psychiatric disorders with all gastrointestinal (GI) disorders

- Many patients with functional GI disorders may experience considerable improvement in their symptoms when a concurrent psychiatric disorder is successfully identified and treated.
- In structural (organic) disorders, the GI symptoms may not change as dramatically when coexisting depression or anxiety is treated, but patients may experience substantial improvement in their health-related quality of life—that is, they can cope with their symptoms, treatment, and lifestyle changes much more successfully

- There is an established literature that demonstrates an association between functional GI disorders and a history of childhood sexual and physical abuse
- Neuroticism, hostility, maladaptive coping and emotional hypersensitivity and personality traits that are commonly observed
- Comorbid psychiatric syndromes, particularly depression ,anxiety and somatization ,are also frequently noted.



gut-brain axis (GBA)

The gut-brain access includes;

- the central nervous system,
- the autonomic nervous system,
- the enteric nervous system,
- and the hypothalamic-pituitary-adrenal (HPA) axis,
- as well as signaling mediated by gut peptides

The role of the GBA

- The role of the GBA is to;
- integrate functional activity in the gut and to link the emotional and cognitive centers in the brain with the peripheral functions of the intestine, along with their mechanisms.
- These include satiety, appetite, immune activation, intestinal permeability, enteroendocrine signaling, and enteric reflexes.

Gastrointestinal disorders

- a group of disorders that affect the gastrointestinal tract, which impacts physiological function concerning the absorption and digestion of food and exerting a significant impact on a patient's health-related quality of life.
- In cases of irritable bowel syndrome, there is no clear pathogenesis. The most common gastrointestinal disorder is irritable bowel syndrome, which predominantly affects the lower gastrointestinal tract.

Irritable Bowel Syndrome

- Symptoms include abdominal pain or discomfort that is relieved by defecation and associated with altered stool frequency or form
- Additional symptoms: flatulence, bloating, stool urgency, persistent sensation of incomplete bowel evacuation

- Subdivided: (bowel pattern) diarrhea, constipation, altering
- Diagnosis: symptomatic history without alarm symptoms (fever, weight loss, rectal bleeding)

The Rome IV criteria

Table 1

IBS Diagnostic Criteria *.

Recurrent abdominal pain on average at least 1 day/week in the last 3 months, associated with two or more of the following criteria:
1. Related to defecation
2. Associated with a change in the frequency of stool
3. Associated with a change in the form (appearance) of stool

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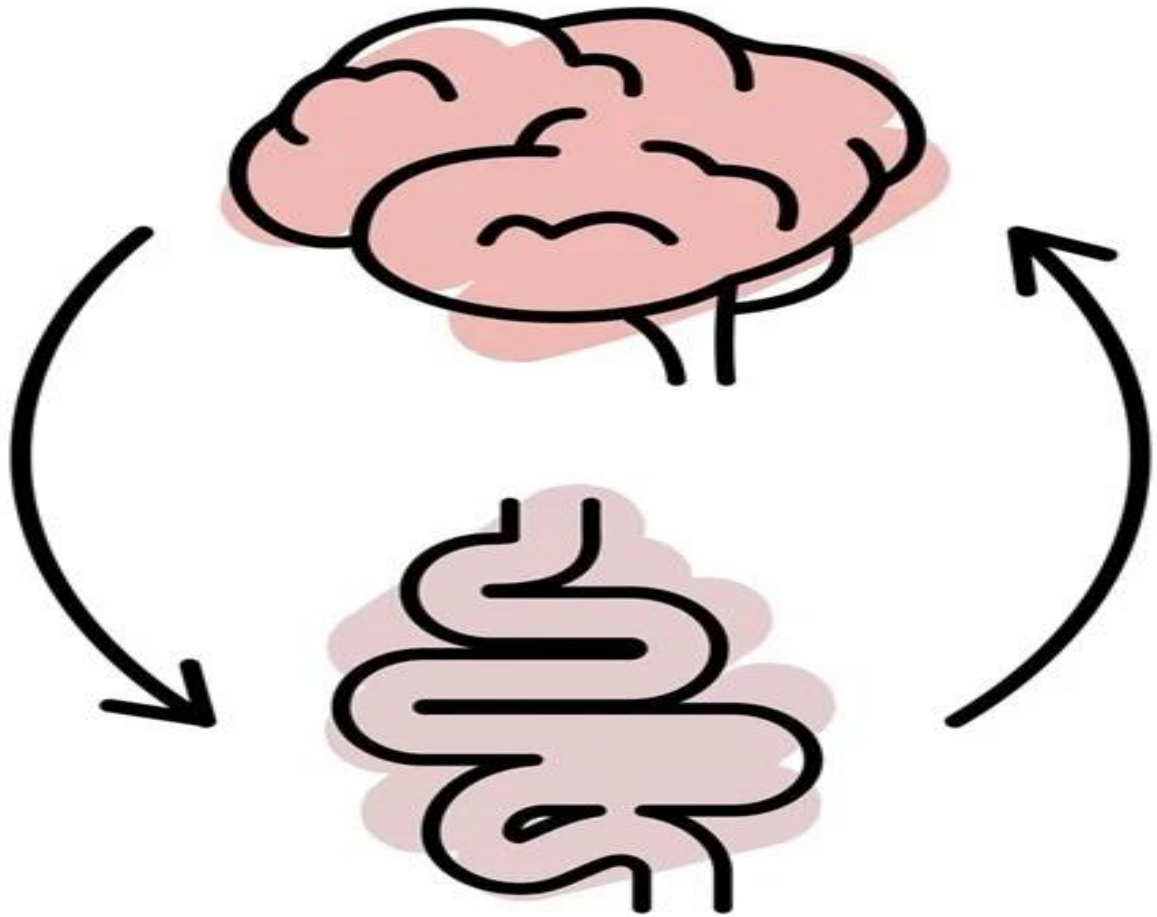
(These criteria should be fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis.) * Modified from Rome IV [9].

IBS

- The prevalence of irritable bowel syndrome varies widely.
- However, it is estimated that the pooled global prevalence is 11.2%,
- with a higher prevalence in women than men.
- Consume 50%more health care costs
- it can dramatically reduce the patient's health-related quality of life.

pathophysiology

- Psychiatric comorbidity is elevated in patients with gastrointestinal disorders,
- suggesting shared or interacting disease mechanisms, which are attributed to the communication between the gastrointestinal system and the brain by the gut-brain axis.
- Within this, different states of the intestinal microbiome are thought to play an essential role.
- Moreover, studies have implicated the role of the vagus nerve, which is the mediator between the gut and the brain.



The microbiota-gut-brain axis and neuropsychiatric disorders

- Humans harbor a unique community of microbiota that is subject to change in composition and abundance by several factors,
- which include exercise, diet, health, stress, age, use of medication, and others.
- The microbiota-gut-brain axis is a dynamic interrelation of the gastrointestinal microbiota, tissues, glands, organs, immune cells, the autonomic nervous system, and the brain.
- Together these **communicate via multi-directional signaling** via anatomically and physiologically distinct systems.

The microbiota-gut-brain axis and neuropsychiatric disorders

- long-term perturbation to this homeostatic environment fostered by the microbiota-gut-brain axis can contribute to the progression of several disorders as a consequence of alterations in several physiological processes,
- including the hypothalamic-pituitary-adrenal axis activation, immune function, and associated inflammatory response, and neurotransmitter systems.

- Under homeostatic conditions, coordinated physiological responses exemplified by an immune or stress response are necessary for survival.
- However, a dysfunctional response can result in adverse effects, resulting in several central nervous system disorders.

- high degree of correlation between stress-related symptoms such as anxiety and irritable bowel syndrome, which provided a basis for implicating the **vagus nerve**.

The microbiota-gut-brain axis and neuropsychiatric disorders

- This was corroborated by additional studies that demonstrated that uncontrolled sympathetic and poor vagus control results in interactions with the microbiome and immune system,

- subsequently predisposed individuals to suffer from psychiatric and gastrointestinal diseases.
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The incidence of psychiatric illness and gastrointestinal disorders

- Approximately 60% of those who suffer from gastrointestinal disorders are found to suffer from one of several psychiatric disorders.
- Among them, depression and anxiety are the most common comorbidities.
- There is a correlation between the two, with patience exhibiting high levels of depression and anxiety possessing a two-fold risk of developing irritable bowel syndrome(IBS) and vice versa

- Among the psychiatric disorders, anxiety is the most strongly implicated in the burden of gastrointestinal symptoms;
- irritable bowel syndrome is strongly correlated with those who have **panic disorder** and **generalized anxiety disorder.**

- recent meta-analysis demonstrated that depression and anxiety alike were increased in all subtypes of irritable bowel syndrome compared with healthy controls

- with the highest level of depression demonstrated in those with constipation-predominant irritable bowel syndrome.

etiology of gastrointestinal disease and mental health comorbidity

- the gut-brain axis is implicated as a central mediator
- Increased sympathetic, decreased parasympathetic, and altered autonomic nervous system activities
- The effects of these factors are augmented by the release of local hormones and information;
- the **vagus** nerve is thought to provide a connection between microbial activity and other metabolites and the central nervous system.

etiology of gastrointestinal disease and mental health comorbidity

- In addition, the HPA axis has also been implicated as observed in IBS patients who demonstrated increased basal cortisol and stress-induced cortisol relative to healthy patients.
- The microbial composition can produce neurologically active substances, f.e, short-chain fatty acids and gamma-aminobutyric acid – but their role in behavioral on psychological alterations is poorly understood.
- short-chain fatty acids can alleviate stress-induced anhedonia and increase responsiveness to stress

etiology of gastrointestinal disease and mental health comorbidity

- Other proposed mechanisms include a breakdown of the mucosal barrier,
- which results in the translocation of bacteria and subsequent activation of the immune response
- which produces excessive cytokines that affect both the function of the gastrointestinal system and the associated microflora, and brain functions and behavior..

etiology of gastrointestinal disease and mental health comorbidity

- Specifically, high levels of pro-inflammatory markers,
- particularly interleukin-1, interleukin-6, and tumor necrosis factor-alpha,
- have been observed in patients suffering from depression;
- this is corroborated by knowledge, but inflammation has the potential to induce depression

MGB axis(Microbiota-Gut-Brain Axis)

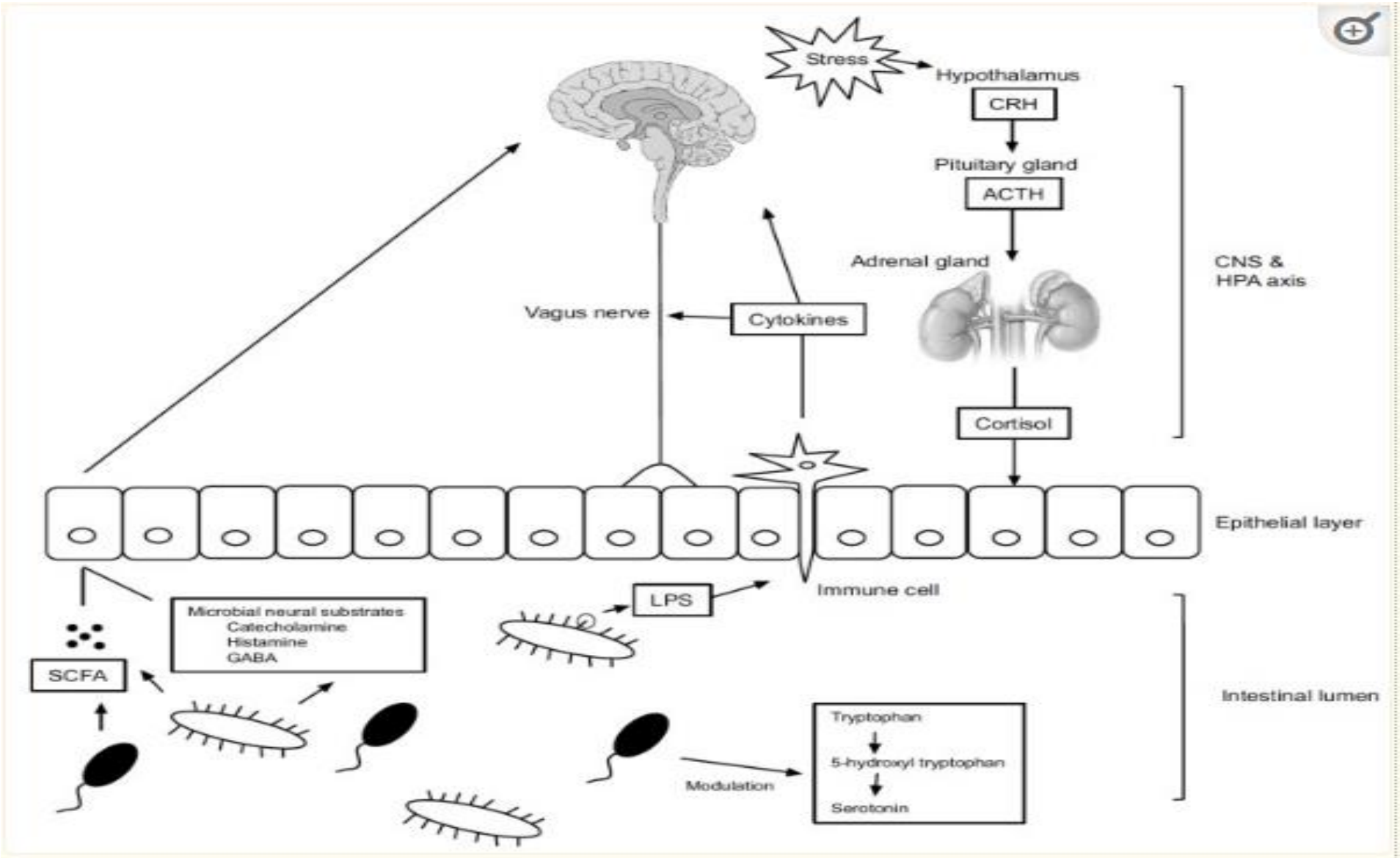
- The MGB axis is part of a comprehensive physiological network including the endocrine system (hypothalamic-pituitary-adrenal axis), the immune system (cytokines, chemokines), the autonomic nervous system (including efferent and afferent neurons), and the enteric nervous system.
- Gut microbiota are thought to act on the hypothalamic-pituitary-adrenal (HPA) axis and the vagus nerve by producing bacterial metabolites ***via*** **tryptophan metabolism**.

MGB

- In a mouse model, even two hours of social disruption altered the profile of the microorganism community, where the *Lactobacillus* population declined

- the *Lactobacillus* concentration in feces was lower in healthy students during a period of extreme stress than during a period of mild stress.

Interaction pathways of the microbiota–gut–brain axis



MGB

- GABA, a major inhibitory neurotransmitter in the CNS whose dysfunction is associated with depression, anxiety, autism, and schizophrenia, is efficiently produced by *Lactobacillus* in human intestines .
- GABA produced by intestinal bacteria crosses the blood-brain barrier (BBB) and enters the CNS
- *Lactobacillus rhamnosus* has been found to reduce anxiety and depression-related behaviors in mice and to increase GABA concentration in the hippocampus.
- intestinal microorganisms indirectly regulate GABA signaling through the vagus nerve.

MGB

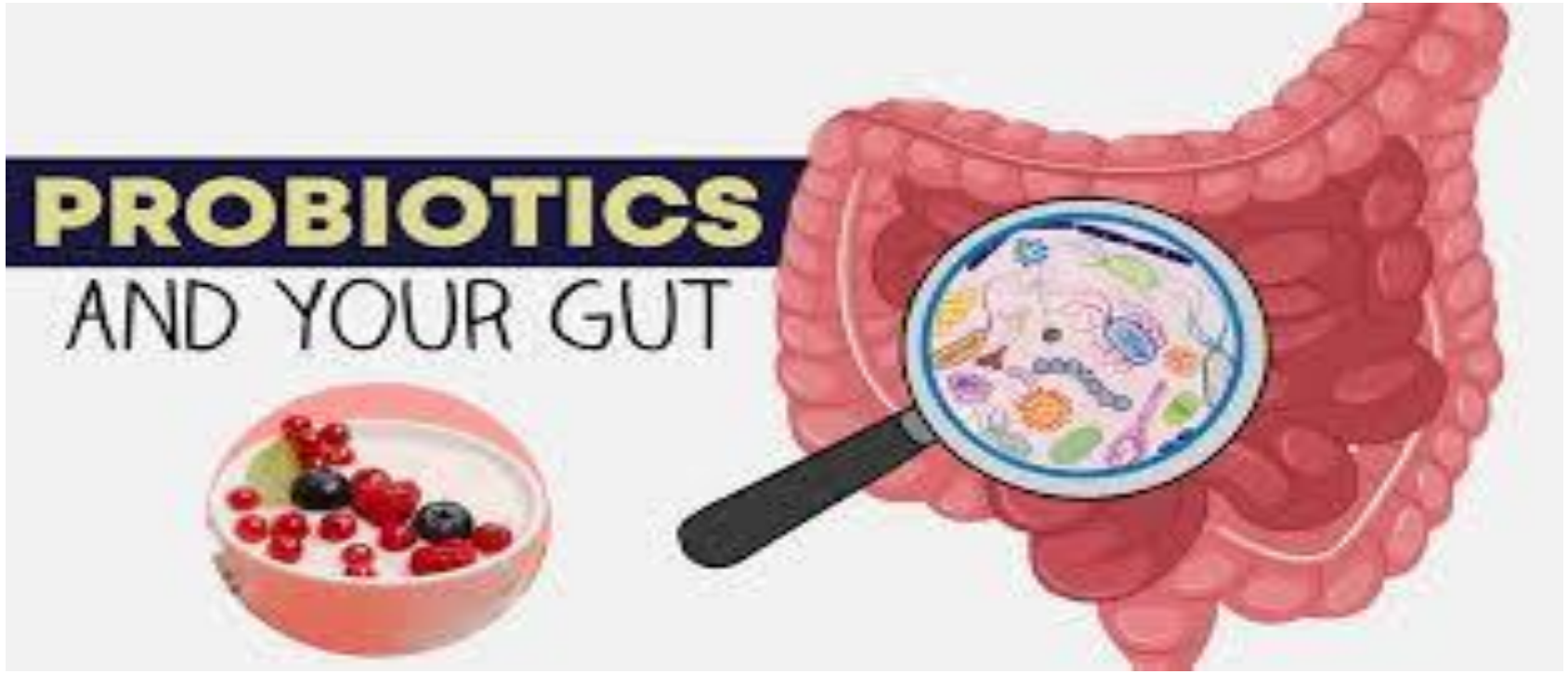
- In contrast, probiotics might ameliorate anxiety.
- Some species of *Lactobacillus* and *Bifidobacterium* have anxiety-relieving effects.
- Probiotic treatment involving specific strains of *B. longum*, *B. infantis*, *L. helveticus*, or *L. rhamnosus* alone or in combination normalized behavioral phenotypes in animal anxiety models via correction of immunologic factors and regulation of GABA receptors

- Depression is a mood disorder associated with imbalance of the HPA axis, dysregulation of the immune system, and deficiency of tryptophan metabolism .
- Although it is not known whether an **imbalance of intestinal microorganisms is the cause or the effect of depression,** several observational studies show a **bidirectional interaction** between depression and the gut microbiome.

- The observation that a malfunctioning intestinal wall or a leaky gut causes inflammation due to microorganisms has been reported
- Under normal conditions, immune cells are separated from intestinal gram-negative bacteria.
- However, when intestinal permeability changes and barrier integrity is disrupted, certain gram-negative bacteria such as *Enterobacteriaceae* are translocated across the barrier, and the inflammatory process is activated

- Such translocation can result in immunoglobulin (IgA and IgM)-mediated immune responses to the LPS of gram-negative bacteria, which can secondarily lead to depression

TREATMENTS TARGETING THE GUT MICRO-BIOTA FOR NEUROPSYCHIATRIC ILLNESSES



- Probiotics are defined as live microorganisms that provide health benefits to humans or animals when consumed.
- *Lactobacillus* and *Bifidobacterium* species account for most probiotics.
- Animal studies on probiotic involvement in various neurological diseases have been performed, and many promising results have been reported.
- Most of these are studies on cognition, autism spectrum disorder, or anxiety and depressive-like behavior

- Studies on probiotics with positive results have shown that low-grade inflammation is reduced, neurotrophic factors such as BDNF are modulated, gut permeability is restored, and the composition of the gut microbiome changes.
- In a six-week clinical trial groups receiving a probiotic capsule or probiotic yogurt showed alleviated anxiety and depression compared to groups receiving a placebo capsule or conventional yogurt

Fecal Microbiota Transplantation



Fecal Microbiota Transplantation

- refers to transplantation of healthy human feces to a suspected gut dysbiosis patient to regulate the intestinal microbiota.
- When the normal gut microbiota are destroyed by antibiotic treatment **, the recovery of normal bacterial flora by FMT can be outstanding** . As a result, interest in FMT has begun to increase.
- FMT can also be an effective treatment for IBS. IBS showed a remission rate of 36-89% after FMT treatment

Psychopharmacological intervention

Antidepressants (TCAs, SSRIs) :

- frequent psychiatric comorbidity
- central effects on pain modulation
- effects on visceral sensitivity

- **TCAs** work in the CNS to blunt pain and other symptoms exacerbated by stress(desipramine)

- **SSRIs** (Serotonin):control of gut function &pain pathways

  along with the AbNl S signaling and release in IBS

  Paroxetine, fluoxetine, citalopram

Psychological intervention

- CBT(first line approach):reduction in hypervigilance to visceral stimuli
- mindfulness
- Psychodynamic therapy
- Hypnosis
- Stress management
- Relaxation therapy

Thank you for your attention

