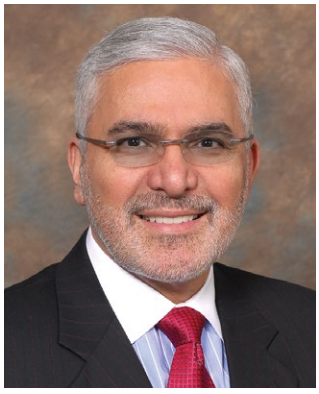

Henry A. Nasrallah, MD
Editor-in-Chief

It takes guts to be mentally ill: Microbiota and psychopathology

What is the largest endocrine organ in the human body?

Here is a clue: It is also the largest immune organ in humans!

Still scratching your head? Here is another clue: This organ also contains a "second brain," which is connected to big brain inside the head by the vagus nerve.

Okay, enough guessing: It's the 30-foot long gastrointestinal (GI) tract, which is generally associated only with eating and digestion. But it is far more than a digestive tract. It is home to about 100 trillion diverse bacteria, including 1,000 known species, which together are known as "microbiota." Its combined DNA is called the "microbiome" and is 10,000% larger than the human genome. Those trillions of bacteria in our guts are a symbiotic (commensal) organ that is vital for the normal functions of the human body.[1]

While this vast array of microorganisms is vital to sustaining a healthy human existence, it can also be involved in multiple psychiatric disorders, including depression, psychosis, anxiety, autism, and attention-deficit/hyperactivity disorder (ADHD). Humans acquire their unique sets of microbiota as they pass through the mother's vagina at birth and while breastfeeding, as well as from exposure to various environmental sources in the first few months of life.[2]

The microbiota in the GI tract are an intimate neighbor of the "enteric brain," comprised of 100 million neurons plus glia-like support cell structures. This "second brain" produces over 30 neurotransmitters, several of which (dopamine, serotonin, γ-aminobutyric acid [GABA], acetylcholine) have been implicated in major psychiatric disorders.[3]

The brain and gut have a dynamic bidirectional communication system, mediated by neural, hormonal, and immunological crosstalk and influences. The GI tract secretes dozens of peptides and other signaling molecules that influence the brain. The microbiota also interact with and are regulated by gut hormones such as oxytocin, ghrelin, neuropeptide Y, cholecystokinin, corticotrophin-releasing factor, and pancreatic polypeptide.[4] The microbiota modulate brain development, functions, and behavior, and maintain the intestinal barrier, which, if disrupted, would result in the gut becoming "leaky" and triggering low-grade inflammation such as that associated with depression.[5]

But don't overlook the importance of diet. It is a major factor in shaping the composition of the microbiota. What we eat can have a preventative or reparative effect on neuroimmune

The discovery of microbiome-gut-brain interactions has been a momentous paradigm shift in health, neuroscience, and psychiatry

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or neuroinflammatory disease. An emerging body of evidence suggests that the diet and its effects on the gut microbiota can modify a person's genes by epigenetic mechanisms (altering DNA methylation and histone effects). Probiotics can exert epigenetic effects by influencing cytokines, by producing short-chain fatty acids (SCFAs), by vitamin synthesis, and by producing several well-known neurotransmitters.[6]

The bidirectional trafficking across the microbiome-gut-brain axis includes reciprocal effects. The brain influences the microbiome composition by regulating satiety, the hypothalamic-pituitary axis, and with neuropeptides.[7] In return, the microbiome conveys information to the brain about the intestinal status via infectious agents, intestinal neurotransmitters and modulators, cytokines, sensory vagal fibers, and various metabolites. Failure of these normal interactions can lead to a variety of pathological processes, including inflammatory, autoimmune, degenerative, metabolic, cognitive, mood, and behavioral adverse effects. Therapeutic interventions for these adverse consequences can be implemented through microbiome manipulations (such as fecal transplants), nutritional strategies, and reinforcement of the enteric and brain barriers.

Alterations in the microbiota, such as by the intake of antibiotics or by intestinal inflammation, can lead to psychiatric disorders.[8] The following findings link gut microbiome disruptions with several psychiatric disorders:

Schizophrenia prodrome. Fecal bacteria show an increase in SCFAs, which can activate microglia (the initial step in triggering psychosis).[9] These bacteria have been shown to lead to an increase in choline levels in the anterior cingulate, a known biomarker for membrane dysfunction, which is one of the biological models of schizophrenia.

Schizophrenia—first-episode. A recent study reported abnormalities in the gut microbiota of patients with first-episode psychosis, with a lower number of certain fecal bacteria (including bifidobacterium, E. coli, and lactobacillus) and high levels of Clostridium coccoides. After 6 months of risperidone treatment, the above changes were reversed.[10]

Another study of fecal microbiota in a first-episode psychosis cohort found significant differences in several bacterial strains compared with a healthy control group, and those with the strongest difference had more severe psychotic symptoms and poorer response after 12 months of antipsychotic treatment.[11]

Autism has been linked to increased microbiota diversity, and an excess of bacteroides has been associated with a higher diversity of autism. Fecal samples from autistic children were reported to have an increase in SCFAs. Interestingly, a certain strain of lactobacillus can modulate oxytocin or reverse some autistic symptoms.

Depression has been associated with increased diversity of microbiota alpha. Patients with depression have been reported to have low numbers of bifidobacterium and lactobacillus. Certain strains have been reported to reduce depression and anxiety behaviors in animal studies. The microbiota-friendly Mediterranean diet, but not the Western diet, appears to mitigate the risk of depression. Certain probiotics have been reported to increase resilience to stress.[12,13]

ADHD. Some studies suggest that ADHD may be linked to factors that can alter gut microbiota, including birthing mode, type of infant feeding, maternal health, and early stressors. In addition, dietary influences on gut microbiota can modify ADHD symptoms.[14]

Alzheimer's disease. Metabolic dysregulation, such as obesity and diabetes, can inflame the gut microbiota, and

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Alterations in the microbiota, such as by the intake of antibiotics or by intestinal inflammation, can lead to psychiatric disorders

are known risk factors for Alzheimer's disease.[15]

Irritable bowel syndrome (IBS). Fecal microbiota transplantation has been shown to improve IBS by increasing the diversity of gut microbiota.[16] It also improves patients' mood, not just their IBS symptoms.

Alcohol use. Both alcohol consumption and alcohol withdrawal have been shown to cause immune dysregulation in the brain leading to neuroinflammation. This is attributed to the alteration in the composition of the microbiome (dysbiosis), which has a negative effect on the microbe-host homeostasis.[17]

The discovery of microbiome-gut-brain interactions and their bidirectional immune, endocrine, and neurotransmitter effects has been a momentous paradigm shift in health, neuroscience, and psychiatry.[18] It has opened wide vistas of research for potential innovations in the prevention and treatment of various psychiatric disorders. Radical medical interventions that were previously inconceivable, such as fecal transplantation,[19] are an example of the bold insights this new field of microbiome-gut-brain interaction is bringing to the landscape of medicine, including psychiatry. It has also highlighted the previously underappreciated importance of nutrition in health and disease.[20]

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