

The Microbiome, Gut-Brain-Axis, and Implications for Brain Health

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Abstract

As Antonio Damasio highlighted back in 1994, Descartes' division of mind and body slowed the full realization of the connectedness of the brain and the body by centuries. The simple fact that homeostasis in the brain is fully interconnected with the body has eluded researchers and clinicians even after the connection was well established. Recent studies reporting the central role in dysfunction of mental systems as a result of inflammation in the gut and the autonomic nervous system (ANS) was yet one more reminder that the entire system is connected and interdependent. Central to this discovery and its application to mental function has been the growing field of study of the microbiome. This article is an attempt to situate those who are active in the variety of ways and means of treating the brain in the essential role that is likely being played by a vast community of bacteria living in the bowels of the human being and influencing all of the higher and most "sophisticated" aspects of human interchange and thought. It is the authors' hope that this brief introduction will remind and inform researchers and clinicians that the organism is more interconnected and more complex than we have tended to think and that disorders of the mind are likely also often disorders of the gut.

Keywords: microbiome; gut-brain-axis; brain health

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The Microbiome

The microbiome can be thought of as the genome of a community of bacteria living mainly in the lower intestine, which has been shown to be associated with a range of concerns including disease susceptibility, immune response, and mental health. More than 1,000 species have been identified in the microbiome, each colony being specific to its host (Collins, Surette, & Bercik, 2012). Factors associated with the type and multitude of bacteria in the gut are a vaginal birth, diet, genetics, environment, and of course antibiotic use.

To understand the importance of the microbiome, one must first understand that the microbiome is thought to communicate directly with the brain

through the so-called gut-brain axis. Specifically, bidirectional signaling between the gastrointestinal tract and the brain is thought to be mandatory for homeostasis and integrates neural, hormonal, and immunological signaling (Collins et al., 2012; Cryan & O'Mahony, 2011). Evidence now suggests that gastrointestinal bacteria have implications for brain function and even behavior (Cryan & O'Mahony, 2011).

Gut microbiota have been shown to have a significant relationship with perception of stress and the ability to handle stressors, although most studies of intestinal microbes and brain function have been carried out in mice. For a thorough review, please see Cryan and O'Mahony (2011). Not only does the link between brain and gut become apparent in

disease states in this literature, additionally the pathway for treatment of disease has been posited as solely through the alteration of the microbiome. Highlights from Cryan and O'Mahony's review include such tidbits as that when intestinal microbes are replaced with intake of probiotics, improvement is seen in diseases such as irritable bowel syndrome and chronic fatigue, and specifically by way of reduction of anxiety and stress response, improvement in mood and a reduction in serum cortisol levels (Logan & Katzman, 2005; Messaoudi et al., 2011; Rao et al., 2009). Probiotic agents such as *Bifidobacterium infantis* have antidepressant properties in a forced swim test, a test commonly used to evaluate the antidepressant properties of pharmacological agents (Desbonnet, Garrett, Clarke, Bienenstock, & Dinan, 2008).

Microbes found in the intestine can alter genetic messages via messenger ribonucleic acid (mRNA), whose principal role is to carry instructions for controlling the synthesis of proteins. mRNA can actively modify central nervous system receptors, including GABA_A and GABA_B (gamma-aminobutyric acid), resulting in hyperpolarization of neurons and inhibition of neurotransmission. In one particularly interesting study, *Lactobacillus reuteri*, known to modulate the immune system through the alteration of mRNA expression of both GABA_A and GABA_B receptors, was associated with decreased anxiety and the reduction of the increase of corticosterone in mice under stress conditions (Bravo et al., 2010).

Autonomic nervous system (ANS) activity from the gut is connected to limbic areas of the brain, specifically the amygdala, hippocampus, and the limbic cortex (Collins et al., 2012). A component of the ANS, the sympathetic system, is thought to exhibit an inhibitory influence on the intestine by decreasing motility and secretion by the release of neurotransmitters such as noradrenaline (Collins et al., 2012). Other activity within the hypothalamic-pituitary-adrenal (HPA) axis, which is responsible for stress responses such as the release of corticosterone and adrenalin, is also modulated by the gut-brain axis, and potentially by the vagus nerve (Collins et al., 2012). For example, Sudo et al. (2004) found germ-free rodents were more susceptible to stress, and more specifically that stress affects their gut bacteria, and bacteria consequently affected how stress was handled. They report a decrease in brain-derived neurotrophic factor (BDNF) in the germ-free rodents, which is involved in neuronal growth in male animals in the cortex and hippocampus.

Stress early in life results in HPA-axis changes centrally, and can have adverse effects in gut microbiota (Desbonnet et al., 2008). This important finding leaves room for exploration of the potential antidepressant effects of probiotics and specifically the attenuation of pro-inflammatory immune responses, the elevation of a serotonergic precursor (tryptophan) by probiotic treatment (Collins et al., 2012). For example, probiotic treatment resulted in a reversal of abnormal immune response, behavioral deficits, and restoration of norepinephrine concentrations in the brainstem (Desbonnet et al., 2010).

Human Research

Microbiome research in human subjects is limited; however, in one study looking at the effects of bacteria on stress, *Lactobacillus helveticus* and *Bifidobacterium longum* were associated with decreased cortisol (a stress hormone; Bravo et al., 2010). A proposed mechanism of the influence of stress on the microbiome, and consequently the gut-brain axis, is that stress has been shown to influence the integrity of the gut epithelium and to alter gut motility, secretions, and mucin production, thereby altering the habitat of resident bacteria and promoting changes in microbial composition or activity (Collins & Bercik, 2009).

The microbiome has been found to be associated with depression, adiposity, immune dysregulation, and eating disorders. Several authors cite the prevalence of psychiatric conditions that often have an associated gastrointestinal condition, such as irritable bowel diseases like Crohn's and ulcerative colitis, which can also be correlated with a disturbance in the microbiome (Cámara, Ziegler, Bégé, Schoepfer, & von Känel, 2009; Collins et al., 2012; Mawdsley & Rampton, 2005, 2006; Wu, 2012). For example, in order to study associations between eating disorders and the microbiome, inpatients diagnosed with anorexia were compared with healthy controls (Kleiman et al., 2015). Stool samples were collected and participants completed self-report measures. Bacterial composition was characterized by gene sequencing and results showed that levels of depression, anxiety, and eating disorder psychopathology were associated with composition and diversity of microbes.

Researchers are now exploring enhanced cognitive effects, reduction of stress and emotional response, and associations with psychological diagnoses and the microbiome. In a study by Tillisch et al. (2013) healthy women were given a nonfermented milk product or no intervention (control group). The women underwent fMRI before and after the intervention to examine resting state activity and responses to an emotional faces attention task. Consumption of a probiotic-enhanced fermented milk product altered brain connectivity in areas responsible for processing emotion and sensation.

There is also research interest in substances that may harm the microbiome, disturb intrinsic balance in the gut-brain axis, and decrease diversity of bacteria. In a recent study, participants were randomly assigned to receive one of four types of antibiotics or placebo (Zaura et al., 2015). Researchers collected fecal samples prior to participants taking antibiotics, immediately after the course of antibiotics, and followed them for 12 months after finishing the antibiotics. Results showed that antibiotics were found to enrich genes associated with antibiotic resistance and to affect microbial diversity for months after the course. Especially concerning was the decline in health-associated species that produces a substance known for inhibition of inflammation, cancer formation, and stress in the gut.

Conclusion

So far, most studies are correlational, making it impossible to draw conclusions about cause and effect. However, from the research-to-date the take home message is to take care of your intestinal microbes—which are likely associated with your overall health, resistance and recovery from disease, cognitive function, and regulation of stress and emotional responses. There are many other examples of this bidirectional communication, certainly enough to make an argument that our gut bacteria should be kept as healthy and as diverse as possible. Out of the approximately 10^{14} microbes estimated to inhabit our intestines at any given time, it is not hard to believe that we co-exist with creatures that have profound implications for our species.

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