

**Title:**

**Microbes on Your Mind.**

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**Abstract:**

The article offers information on the role played by the microorganisms on the moods and thought processing of the human brain. It states that composed mostly of bacteria but also viruses and fungi, the so-called gut microbiota churns out a complex cocktail of biologically active compounds. It mentions that gut microbes could also account for some of the differences in mood, personality and thought processes that occur within and among individuals.

**Microbes on Your Mind**

**Bacteria in your gut may be influencing your thoughts and moods**

The thought of parasites preying on your body or brain very likely sends shivers down your spine. Perhaps you imagine insectoid creatures bursting from stomachs or a malevolent force controlling your actions. These visions are not just the night terrors of science-fiction writers -- the natural world is replete with such examples.

Take *Toxoplasma gondii*, the single-celled parasite. When mice are infected by it, they suffer the grave misfortune of becoming attracted to cats. Once a cat inevitably consumes the doomed creature, the parasite can complete its life cycle inside its new host. Or consider *Cordyceps*, the parasitic fungus that can grow into the brain of an insect. The fungus can force an ant to climb a plant before consuming its brain entirely. After the insect dies, a mushroom sprouts from its head, allowing the fungus to disperse its spores as widely as possible.

Microbes that manipulate the behavior of their host are not limited to nature's dark corners, although those examples are vivid. Our body hosts vast numbers of foreign microorganisms, some of which wield unseen powers over us. These microbes are not parasites -- they live on and in our body, mostly in our gut, and often strike up a symbiotic relationship with us.

Composed mostly of bacteria but also viruses and fungi, this so-called gut microbiota churns out a complex cocktail of biologically active compounds. Some of these products closely resemble human hormones and neurotransmitters, the chemicals that neurons use to communicate with one another. Microbes in the gut (the small and large intestines and the stomach) have long been known to play a role in human health. Irritable bowel syndrome and stomach ulcers, for example, are linked to an imbalanced microbial population.

In the past few years scientists have been discovering that these microscopic inhabitants of our body may be subtly altering our moods, emotions and perhaps even our personalities. Gut microbiota appear to alter gene activity in the brain and the development of key regions involved in memory and learning. These denizens of our intestines could help explain why psychiatric symptoms vary among individuals, as well as their responses to medications. Gut microbes could also account for some of the differences in mood, personality and thought processes that occur within and among individuals.

Early clinical trials are even suggesting that probiotic supplements could treat mood disorders. Eventually we may learn that our bacterial soup contains markers for diseases, which could be detected cheaply and quickly. "Research into the gut microbiome has the potential to change many aspects of health and biotechnology," says molecular biophysicist Rob Knight of the University of Colorado at Boulder.

## Your Microbial Self

From the minute you are born, microbes begin to colonize every exposed surface and organ of your body. By age three the gut contains a full complement of approximately 100 trillion microbes. According to most estimates, about 500 different bacterial species call your intestines home, with 30 to 40 species making up the bulk of the population. Family members' microbial compositions are more similar to one another than to unrelated people, and identical twins are most alike of all, suggesting that genetics helps to determine the intestinal inhabitants we acquire.

The variety among people can be glimpsed with something as simple as a swab of your computer keyboard. In 2010 Knight and his colleagues showed that the bacteria on a computer keyboard resembled the bacterial community on that computer user's fingers more closely than the populations dwelling on a different keyboard or another person's hand. The genomes of these microorganisms harbor approximately 100 times more genes than our own DNA. "Ninety percent of the cells in what we like to think of as 'our' bodies actually contain microbial genomes rather than human ones," he says.

The study of the gut's ecosystem is in its infancy, but interest in this area has been growing rapidly. Drastic reductions in the cost of DNA sequencing allow researchers to analyze large numbers of microbes simultaneously rather than having to grow them one at a time in the laboratory. Scientists can now quickly take a census of the gut and hunt for associations between microbiota and disease.

In 2007 the National Institutes of Health launched the Human Microbiome Project, a five-year, \$115-million initiative to sequence the DNA of as many gut microbes as possible. The following year two more groups were created: the International Human Microbiome Consortium, which seeks to build a comprehensive database, and Meta HIT, an alliance of 13 partners drawn from eight European countries in academia and industry, with \$43 million in funding. These projects all seek to understand how the species populating our gut relate to our health.

The composition of these communities is highly dynamic throughout life. Changes in diet, drugs and other environmental factors can unleash earthquakes on our internal ecosystem. But freeloaders they are not. Bacteria help us digest food by fermenting dietary proteins and polysaccharides. They synthesize amino acids and minerals that the body needs but does not produce itself, and they protect us from pathogens by interacting with the immune system. Microbiome diversity appears to be a good indicator of general health -- it decreases with age, and people with reduced diversity not only put on weight more easily than others but also struggle more to lose a few pounds. It should come as no surprise, then, that these microscopic creatures also meddle with the mind.

## The Gut-Brain Connection

Anyone who has ever lost control of their bowels when scared is well aware of the intimate connection between the brain and the body's internal plumbing. We refer to "gut feelings" to describe an intuitive, emotional response, and we say that doing something daring "takes guts." Less obvious is that these responses are not merely emanating from a single lump of flesh, sophisticated as it may be.

Embedded in the lining of the intestines is the enteric nervous system, with hundreds of millions of neurons -- one-thousandth the number in your brain. This network, colloquially termed a "second brain," controls gut function. It processes messages from the intestines and their microbes without input from brain number one. Gut neurons communicate with the brain through the vagus nerve, which extends from the base of the brain to the chest and abdomen and sends a branch of nerve fibers to the intestines.

The clearest connection between gut bacteria and the mind can be seen in how we experience anxiety and stress. In one influential study in 2004, for example, Nobuyuki Sudo of Kyushu University in Japan and his colleagues speculated that microbes might be involved in the brain's stress response. They had previously shown that gut microbes affect the development of the immune system early in life. The immune system, in turn, interacts extensively with the nervous system during this period. To investigate, they raised newborn mice in special conditions that prevented microbes from colonizing their guts. The rodents were then placed in situations designed to induce stress, in this case by restraining them. Compared

with normal mice, the germ-free mice had higher levels of stress hormones in their blood and reduced expression of the gene that codes for brain-derived neurotrophic factor (BDNF) in the hippocampus, a region important for memory formation and learning. When the brain generates new neurons, those young cells grow axons and dendrites that seek out networks of existing neurons to join. Those that encounter a burst of the protein BDNF during this process are more likely to survive and link up with other neurons; those that do not will wither away. Sudo's experiment suggested that gut microbes could influence the growth of memory and learning networks, which affected the rodents' ability to handle stress.

To strengthen the argument that microbes might be responsible for the changes, the researchers then colonized the germ-free mice with *Bifidobacterium infantis*, one of the most prevalent species in the microbiota and one of the first bacterial strains to settle into the gut of newborns, both human and rodent. The newly infected rodents' stress response quieted down to match that of the normal mice.

John Bienenstock and Jane Foster of the Brain-Body Institute at McMaster University in Ontario recently revisited this idea in a series of studies published in 2011. In one experiment they infected mice with a parasite that is known to induce those same effects -- heightened anxiety and reduced activity of the BDNF gene in the brain. When they then introduced *Bifidobacterium longum* -- another early colonizer of the gut after birth -- into the mice, the parasite's effects disappeared. Somehow gut microbes seemed to be helping out the rodents' brain.

Gut bacteria are notoriously difficult to study, however. Not only are researchers mostly dependent on animal models, even creating the conditions needed to test those animals can be extremely tricky. Raising rodents free of microbes requires special facilities and equipment. In addition, labs can differ in the bacteria that inhabit their normal, or control, mice. These variations in difficult-to-track microscopic conditions can lead to seemingly conflicting results. The overall message, however, is that gastrointestinal microbes can change animals' emotional responses, although whether those results are positive or negative may depend on the environment both inside and surrounding the gut.

For example, Bienenstock, Foster and their collaborators recently compared the behaviors of germ-free mice with normal mice. These germ-free mice were less anxious than the control rodents. They also saw brain changes to match those outcomes -- namely, more expression of the gene encoding BDNF in the germ-free mice and fewer receptors for the neurotransmitters serotonin in the hippocampus and glutamate in the amygdala, a brain region that processes emotions. Serotonin is a key player in mood. Glutamate, like BDNF, is critical to learning and memory, suggesting that gut bacteria might have some effect on cognitive processes beyond mood. Yet when the researchers then tried to introduce microbes into adult germ-free mice, they observed no changes to behavior. This finding implies that the microbes exert their effects during a limited developmental time window. A second, similar study of theirs, using a different microbe, found altered expression of the genes relating to another important neurotransmitter, GABA, throughout the brain. The receptors for this chemical are a target for a class of drugs commonly used to treat anxiety, including Valium.

To get a more fine-grained view, the researchers dissected a mouse's myenteric plexus, a major component of the gut's nerve network. They inserted microelectrodes into individual neurons to record the cells' responses to various bacteria. These recordings revealed that some strains of *Bifidobacterium* and *Lactobacillus*, among the most prevalent bacterial species in the human gut, could block those neurons from producing impulses and lower the rodent's visible response to abdominal pain.

Bienenstock and his colleagues speculated that these neural changes might reach the brain by way of the vagus nerve. Indeed, severing this nerve in rodents abolished the microbes' effects. A second possible line of communication has also emerged in preliminary results presented at the Microbes for Health symposium in Paris last December: some strains of gut bacteria produce short-chain fatty acids that can increase the permeability of the blood-brain barrier. These molecules might alter which substances in the bloodstream can enter the brain.

As strong as the connection may seem in rodents, similar experiments in humans are lacking, leaving many open questions about what those intestinal interlopers might be doing in more complex organisms. "The findings are intriguing, but the

details of what will generalize to humans requires detailed further study," Knight says. "We know that microbes influence gene expression in many tissues, so it would be a surprise if the brain were an exception." Emeran Mayer, a professor of neurogastroenterology at the David Geffen School of Medicine, U.C.L.A., is more hesitant. Researchers do not have the opportunity to raise babies in sterile environments, nor is our nervous system as simple as a rat's. "Given the robustness of the effects, one would expect that some of them also occur in humans, particularly in the early life periods," he says. "But there is a major difference between the rodent and human brain -- they do not have our extensive prefrontal cortex."

### **Probiotics for Your Brain**

Evidence supporting a connection between gut ecology and the human brain is now trickling in. One example comes from infants -- colicky babies have less diversity in their gut microbiota than is normal at that age and seem to be predisposed to stress later on. S Other data are emerging from clinical trials of probiotic supplements -- the microorganism-filled tablets and cultures, such as those added to yogurt, that are believed to aid digestion.

In 2011 French researchers published the results of a small clinical trial examining the antianxiety effects of probiotics. They had 66 patients take either a placebo or a probiotic formulation containing *Lactobacillus helveticus* and *B. longum*, two common inhabitants of guts, for a month. The participants were evaluated for anxiety and depression according to widely accepted checklists at the beginning and again at the end of the experiment. At the end of the month the group that took the probiotics showed the greatest decrease in signs of psychological distress as measured through the participants' self-reports.

Those findings are in line with what others have observed. In a paper currently in press, Mayer and his U.C.L. A. colleague Kirsten Tillisch worked with 45 healthy female volunteers to assess the effects of taking a probiotic formulation for a month. They divided the participants into three groups: 13 subjects were given a probiotic dairy product, another group received a milk-based, nonfermented dairy product, and the remaining women took nothing.

When they scanned each woman's brain, they found that compared with the two control groups, the participants given probiotics had significantly less resting-state activity -- the brain's firing patterns when thinking about nothing in particular -- as well as a dampened response in their arousal networks, which includes the amygdala, in response to emotional faces. "We have several other studies either ongoing or in the planning phase all aimed at investigating if chronic probiotic intake or reduction of gut microbes by antibiotics can alter human brain structure and function," Mayer says.

Ultimately the concept of the gut-brain connection will very likely prove too simplistic. A fuller understanding of the effect of microorganisms on the psychological landscape will take into account chatter among other organs and systems in the body and their respective microbial communities. For example, acne has long been associated with anxiety and depression, and in 1930 dermatologists John Stokes and Donald Pillsbury put forward the "gut-brain-skin axis" hypothesis to explain the link. They proposed that emotional states might alter gut microbiota, which could increase the gut's permeability and lead to skin inflammation. They also advocated a probiotic remedy -- a milk preparation containing *Lactobacillus acidophilus*, the common additive in dairy products. Bienenstock's group recently found evidence for this idea, showing that *Lactobacillus* soothes skin inflamed by stress and restores normal hair growth in mice.

We may yet discover that the microbes on our skin can communicate with those in our gut to influence our behavior. "It's not unreasonable to think that microbes elsewhere are involved," Bienenstock says. "Could we have some microbial ointment that improves health and well-being? The mind boggles at the possibilities."

Our bacterial soup may contain markers for diseases, which could one day be detected cheaply and quickly.

In mice, microbes can soothe skin inflamed by stress, suggesting a link between the gut, brain and skin.

### **FAST FACTS**

#### **Moody Microorganisms**

1. >> Bacteria and viruses dwelling in our gut produce compounds that can interact with our nervous system in ways that appear to affect our anxiety and stress responses.
2. >> Early clinical trials suggest that bacterial remedies, such as probiotic supplements, may be useful in treating several types of psychological distress.
3. >> Eventually individual assessments of gut microbial communities could allow physicians and researchers to tailor treatments for mental disorders.

The green cells shown above are in the process of developing into enteric neurons (red), which control gut function independently of the brain.

The gut may have a sensitive period early in life, when the colonization by gut microbes has a strong effect on behavior, whether for good or ill.

Some beneficial microbes, such as *Lactobacillus*, shown below, are often added to yogurts. In addition to aiding digestion, they may also alter moods.

### **(Further Reading)**

\* *The Second Brain: A Groundbreaking New Understanding of Nervous Disorders of the Stomach and Intestine*. Michael Gershon. Harper Perennial, 1999.

\* *Gut Feelings: The Emerging Biology of Gut-Brain Communication*. Emeran Mayer In *Nature Reviews Neuroscience*, Vol. 12, No. 8, pages 453-466; August 2011.

\* *Regulation of the Stress Response by the Gut Microbiota: Implications for Psychoneuroendocrinology*. T. G. Dinan and J. F. Cryan In *Psychoneuroendocrinology*. Published online April 4, 2012.

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