When Gut Bacteria Change Brain Function

Some researchers believe that the microbiome may play a role in regulating how people think and feel.

David Kohn
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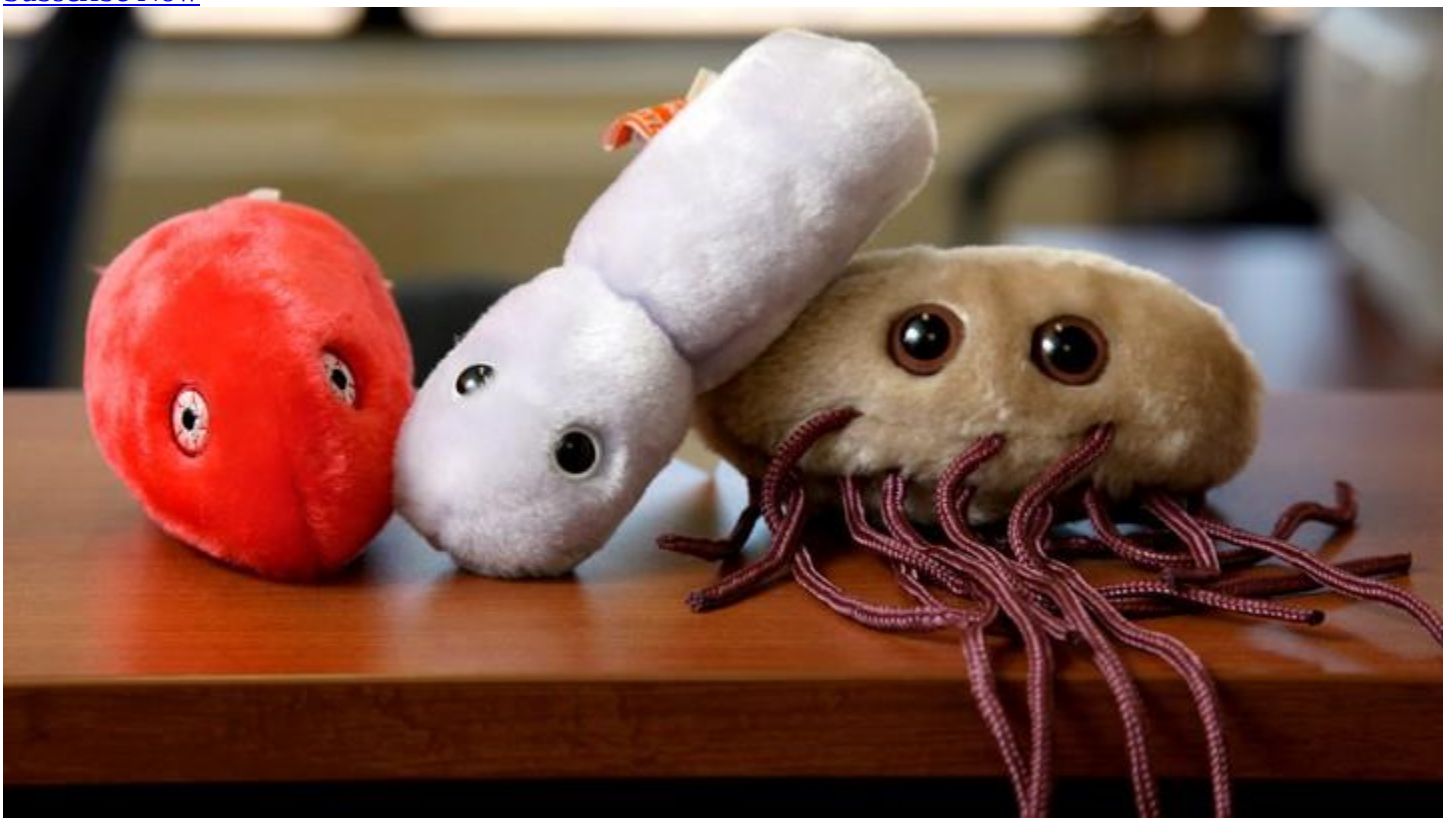

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By now, the idea that gut bacteria affect a person's health is not revolutionary. Many people know that these microbes influence digestion, allergies, and metabolism. The trend has become almost commonplace: New books appear regularly detailing precisely which diet will lead to optimum bacterial health.

But these microbes' reach may extend much further, into the human brains. A growing group of researchers around the world are investigating how the microbiome, as this bacterial ecosystem is known, regulates how people think and feel. Scientists have found evidence that this assemblage—about a thousand different species of bacteria, trillions of cells that together weigh between one and three pounds—could play a crucial role in autism, anxiety, depression, and other disorders.

"There's been an explosion of interest in the connections between the microbiome and the brain," says Emeran Mayer, a gastroenterologist at the University of California, Los Angeles, who has been studying the topic for the past five years.

Some of the most intriguing work has been done on autism. For decades, doctors, parents, and researchers have noted that about three-quarters of people with autism also have some gastrointestinal abnormality, like digestive issues, food allergies, or gluten sensitivity. This recognition led scientists to examine potential connections between gut microbes and autism; several recent studies have found that autistic people's microbiome differs significantly from control groups. The California Institute of Technology microbiologist Sarkis Mazmanian has focused on a common species called *Bacteroides fragilis*, which is seen in smaller quantities in some children with autism. In a paper published two years ago in the journal *Cell*, Mazmanian and several colleagues fed *B. fragilis* from humans to mice with symptoms similar to autism. The treatment altered the makeup of the animals' microbiome, and more importantly, improved their behavior: They became less anxious, communicated more with other mice, and showed less repetitive behavior.

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Exactly how the microbes interact with the illness—whether as a trigger or as a shield—remains mostly a mystery. But Mazmanian and his colleagues have identified one possible link: a

chemical called 4-ethylphenylsulphate, or 4EPS, which seems to be produced by gut bacteria. They've found that mice with symptoms of autism have blood levels of 4EPS more than 40 times higher than other mice. The link between 4EPS levels and the brain isn't clear, but when the animals were injected with the compound, they developed autism-like symptoms.

Mazmanian, who in 2012 was awarded a MacArthur grant for his microbiome work, sees this as a "potential breakthrough" in understanding how microbes contribute to autism and other neurodevelopmental disorders. He says the results so far suggest that adjusting gut bacteria could be a viable treatment for the disease, at least in some patients. "We may be able to reverse these ailments," he says. "If you turn off the faucet that produces this compound, then the symptoms disappear. That's what we see in the mouse model."

Scientists have also gathered evidence that gut bacteria can influence anxiety and depression. Stephen Collins, a gastroenterology researcher at McMaster University in Hamilton, Ontario, has found that strains of two bacteria, *lactobacillus* and *bifidobacterium*, reduce anxiety-like behavior in mice (scientists don't call it "anxiety" because you can't ask a mouse how it's feeling). Humans also carry strains of these bacteria in their guts. In one study, he and his colleague collected gut bacteria from a strain of mice prone to anxious behavior, and then transplanted these microbes into another strain inclined to be calm. The result: The tranquil animals appeared to become anxious.

Overall, both of these microbes seem to be major players in the gut-brain axis. John Cryan, a neuroscientist at the University College of Cork in Ireland, has examined the effects of both of them on depression in animals. In a 2010 paper published in *Neuroscience*, he gave mice either *bifidobacterium* or the antidepressant Lexapro; he then subjected them to a series of stressful situations, including a test which measured how long they continued to swim in a tank of water with no way out. (They were pulled out after a short period of time, before they drowned.) The microbe and the drug were both effective at increasing the animals' perseverance, and reducing levels of hormones linked to stress. Another experiment, this time using *lactobacillus*, had similar results. Cryan is launching a study with humans (using measurements other than the forced swim test to gauge subjects' response).

So far, most microbiome-based brain research has been in mice. But there have already been a few studies involving humans. Last year, for example, Collins transferred gut bacteria from anxious humans into "germ-free" mice—animals that had been raised (very carefully) so their guts contained no bacteria at all. After the transplant, these animals also behaved more anxiously.

Other research has examined entire humans, not just their bugs. A paper published in the May 2015 issue of *Psychopharmacology* by the Oxford University neurobiologist Phil Burnet looked at whether a prebiotic—a group of carbohydrates that provide sustenance for gut bacteria—affected stress levels among a group of 45 healthy volunteers. Some subjects were fed 5.5 grams of a powdered carbohydrate known as galactooligosaccharide, or GOS, while others were given a placebo. Previous studies in mice by the same scientists had shown that this carb fostered growth of *Lactobacillus* and *Bifidobacteria*; the mice with more of these microbes also had

increased levels of several neurotransmitters that affect anxiety, including one called brain-derived neurotrophic factor.

In this experiment, subjects who ingested GOS showed lower levels of a key stress hormone, cortisol, and in a test involving a series of words flashed quickly on a screen, the GOS group also focused more on positive information and less on negative. This test is often used to measure levels of anxiety and depression, since in these conditions anxious and depressed patients often focus inordinately on the threatening or negative stimuli. Burnet and his colleagues note that the results are similar to those seen when subjects take anti-depressants or anti-anxiety medications.

Perhaps the most well-known human study was done by Mayer, the UCLA researcher. He recruited 25 subjects, all healthy women; for four weeks, 12 of them ate a cup of commercially available yogurt twice a day, while the rest didn't. Yogurt is a probiotic, meaning it contains live bacteria, in this case strains of four species, *bifidobacterium*, *streptococcus, lactococcus,* and *lactobacillus*. Before and after the study, subjects were given brain scans to gauge their response to a series of images of facial expressions—happiness, sadness, anger, and so on.

To Mayer's surprise, the results, which were published in 2013 in the journal *Gastroenterology*, showed significant differences between the two groups; the yogurt eaters reacted more calmly to the images than the control group. "The contrast was clear," says Mayer. "This was not what we expected, that eating a yogurt twice a day for a few weeks would do something to your brain." He thinks the bacteria in the yogurt changed the makeup of the subjects' gut microbes, and that this led to the production of compounds that modified brain chemistry.

It's not yet clear how the microbiome alters the brain. Most researchers agree that microbes probably influence the brain via multiple mechanisms. Scientists have found that gut bacteria produce neurotransmitters such as serotonin, dopamine and GABA, all of which play a key role in mood (many antidepressants increase levels of these same compounds). Certain organisms also affect how people metabolize these compounds, effectively regulating the amount that circulates in the blood and brain. Gut bacteria may also generate other neuroactive chemicals, including one called butyrate, that have been linked to reduced anxiety and depression. Cryan and others have also shown that some microbes can activate the vagus nerve, the main line of communication between the gut and the brain. In addition, the microbiome is intertwined with the immune system, which itself influences mood and behavior.

This interconnection of bugs and brain seems credible, too, from an evolutionary perspective. After all, bacteria have lived inside humans for millions of years. Cryan suggests that over time, at least a few microbes have developed ways to shape their hosts' behavior for their own ends. Modifying mood is a plausible microbial survival strategy, he argues that "happy people tend to be more social. And the more social we are, the more chances the microbes have to exchange and spread."

As scientists learn more about how the gut-brain microbial network operates, Cryan thinks it could be hacked to treat psychiatric disorders. "These bacteria could eventually be used the way we now use Prozac or Valium," he says. And because these microbes have eons of experience modifying our brains, they are likely to be more precise and subtle than current pharmacological

approaches, which could mean fewer side effects. “I think these microbes will have a real effect on how we treat these disorders,” Cryan says. “This is a whole new way to modulate brain function.”