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Theese folks can't get things published except in the psychology journals - no one is putting the bigger picture together which is that we may not need antibiotics, psych meds or other bad treatments. the answer is mediated by the gut (in the big picture) and the microbiome (as small picture)

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That gut feeling

With a sophisticated neural network transmitting messages from trillions of bacteria, the brain in your gut exerts a powerful influence over the one in your head, new research suggests.

By Dr. Siri Carpenter
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If aliens were to swoop in from outer space and squeeze a human down to see what we're made of, they would come to the conclusion that cell for cell, we're mostly bacteria. In fact, single-celled organisms—mostly bacteria—outnumber our own cells 10 to one, and most of them make their home in the gut. The gut, in turn, has evolved a stunningly complex neural network capable of leveraging this bacterial ecosystem for the sake of both physical and psychological well-being.

The idea that bacteria teeming in the gut—collectively known as the microbiome—can affect not only the gut, but also the mind, "has just catapulted onto the scene," says neuroimmunologist John Bienenstock, MD, of McMaster University in Hamilton, Ontario. In just the last few years, evidence has mounted from studies in rodents that the gut microbiome can influence neural development, brain chemistry and a wide range of behavioral phenomena, including emotional behavior, pain perception and how the stress system responds.

Research has found, for example, that tweaking the balance between beneficial and disease-causing bacteria in an animal's gut can alter its brain chemistry and lead it to become either more bold or more anxious. The brain can also exert a powerful influence on gut bacteria; as many studies have shown, even mild stress can tip the microbial balance in the gut, making the host more vulnerable to infectious disease and triggering a cascade of molecular reactions that feed back to the central nervous system.

Such findings offer the tantalizing possibility of using beneficial, or probiotic, bacteria to treat mood and anxiety disorders—either by administering beneficial microbes themselves or by developing drugs that mimic their metabolic functions. The new research also hints at new ways of managing chronic gastrointestinal (GI) disorders that are commonly accompanied by anxiety and depression, and that also appear to involve abnormal gut microbiota.

As exciting as these investigations may be, research on how gut bacteria affect psychological well-being in humans is still in its infancy. For one, the studies have been almost entirely limited to rodents. Second, researchers have only begun to probe how such effects occur. Finally, correcting microbial imbalances to treat disease requires first defining what constitutes a healthy gut microbiome—something that scientists are still trying to understand.

"We're just scraping the surface," says McMaster University gastroenterologist Premysl Bercik, MD. "Definitely the animal data suggest that bacteria can have profound effects on behavior and brain biochemistry, probably through multiple pathways." Untangling those biological processes and learning how to apply that knowledge to boost human psychological health will take many years.

The life inside

The human gut is an amazing piece of work. Often referred to as the "second brain," it is the only organ to boast its own independent nervous system, an intricate network of 100 million neurons embedded in the gut wall. So sophisticated is this neural network that the gut continues to function even when the primary neural conduit between it and the brain, the vagus nerve, is severed. (Citing the enteric nervous system's autonomy and apparent infallibility, comedian Stephen Colbert once christened the gut "the pope of your torso.")

At birth, every gut is sterile. But over time, everyone's gut develops a diverse and distinct brew of bacterial species, determined in part by genetics and in part by what bacteria live in and on those around us. The 100 trillion microbes that make the GI tract their playground are critical to health. Gut bacteria regulate digestion and metabolism. They extract and make vitamins and other nutrients from food that you eat. They program the body's immune system. They build and maintain the gut wall, which protects the body from outside invaders. And by their very presence, beneficial bacteria in the gut block harmful microbes from setting up camp and produce anti-microbial chemicals that defend the host against pathogens.

Gut bacteria also produce hundreds of neurochemicals that the brain uses to regulate basic physiological processes as well as mental processes such as learning, memory and mood. For example, gut bacteria manufacture about 95 percent of the body's supply of serotonin, which influences both mood and GI activity.

When you consider the gut's multifaceted ability to communicate with the brain, along with its crucial role in defending the body against the perils of the outside world, "it's almost unthinkable that the gut is not playing a critical role in mind states," says gastroenterologist Emeran Mayer, MD, director of the Center for Neurobiology of Stress at the University of California, Los Angeles.

Indeed, a flurry of studies in the past several years indicates that the gut microbiome's importance goes beyond physical health: It is also a key player in the gut-brain connection. In one striking demonstration of the potency of the so-called "microbiome-gut-brain axis," published in *Gastroenterology* in 2011, Bercik and colleagues gave BALB/c mice, a strain of mice that are typically timid and shy, a cocktail of antibiotics, dramatically changing the composition of their gut bacteria.

"Their behavior completely changed," Bercik says. "They became bold and adventurous."

The antibiotic treatment also boosted levels of brain-derived neurotrophic factor (BDNF) in the hippocampus. This neurochemical promotes neural connections and is an important factor in memory and mood. When the antibiotic regimen was stopped, the animals soon reverted to their usual, cautious selves, and their brain biochemistry also returned to normal.

In a follow-up experiment, Bercik's team corralled two strains of mice born and raised in a sterile environment: timid BALB/c mice, and NIH Swiss mice, known for their courageous, exploratory behavior. The researchers then colonized each group of these "germ-free" mice with bacteria from mice of the opposite strain. The result of this microbial swap was uncanny: The normally anxiety-prone BALB/c mice became much more fearless explorers, while the typically daring NIH Swiss mice suddenly grew more hesitant and shy. The results, Bercik says, underscore that at least in laboratory mice, some seemingly intrinsic characteristics are driven not solely by the animals themselves, but also by microbes inhabiting the gut. Whether the pattern holds up in humans, whose guts harbor more diverse microbial communities, remains to be seen, Bercik says.

It doesn't necessarily take a full-scale microbial transplant to trigger behavioral change. The addition of a single bacterial strain can also change mouse behavior. In one of the earliest studies showing that adding a single bacterium can influence behavior, microbiologist Mark Lyte, PhD, of Texas Tech University Health Sciences Center, and colleagues stirred a small dose of the pathogenic bacterium *Campylobacter jejuni*—too little to trigger an immune response—into saline solution and fed it to a group of lab mice. The results, published in *Physiology and Behavior* in 1998, showed that two days later, mice that consumed the bacteria were more cautious about entering exposed areas of a laboratory maze—a common measure of anxiety in rodents—compared with mice in a control group.

Probiotic promise

While harmful bacteria can ramp up anxiety, several studies have shown that beneficial bacteria can cause anxiety-prone mice to calm down. In a 2011 study published in the *Proceedings of the National Academy of Sciences*, for example, Bienenstock and colleagues fed one group of BALB/c mice broth laced with *Lactobacillus rhamnosus*, a microbe frequently touted for its probiotic qualities. Mice in a control group got just broth, with no microbial bonus. After 28 days, the researchers ran the mice through a battery of tests to detect signs of anxiety or depression.

Compared with mice in the control group, those fed Lactobacillus were more willing to enter exposed areas of a maze, and also less likely to give up and just start floating when subjected to a "forced-swim" test—a test that serves as a mouse analog of some aspects of human depression. The probiotic diet also blunted animals' physiological responses to the stress of the forced-swim test, causing them to produce lower levels of the stress hormone corticosterone. And in the mice fed *Lactobacillus*, some brain regions showed an increase in the number of receptors for gamma-aminobutyric acid, or GABA—a neurotransmitter that mutes neuronal activity, keeping anxiety in check.

Many researchers have wondered whether beneficial gut bacteria might temper the anxiety and depression that often accompany GI disorders such as Crohn's disease, ulcerative colitis and irritable bowel syndrome (IBS). Bercik and colleagues investigated that question in a 2010 study published in Gastroenterology. They first infected mice with a parasite to induce chronic, low-grade gut inflammation. In addition to causing intestinal inflammation, this treatment suppressed levels of BDNF in the hippocampus and caused the mice to behave more anxiously. When mice were then treated to a 10-day course of the beneficial microbe Bifidobacterium longum, their behavior normalized, as did their BDNF levels.

How could gut bacteria influence the brain and behavior so profoundly? One way, some studies indicate, is by co-opting the immune system itself, using immune cells and the chemicals they synthesize to send messages to the brain. But as Lyte's 1998 study showed, some bacteria can induce behavioral changes even without triggering an immune response, suggesting that other channels of gut-brain communication must be at work. In other studies, Bienenstock and others have found that at least in some cases, bacteria communicate with the brain via the vagus nerve: When the vagus nerve is severed, effects of gut bacteria on brain biochemistry, stress response and behavior evaporate. Those findings not only shed light on how bacteria may influence the brain, but also fit with other work in humans that suggests that vagal stimulation can be used as a last resort for treating depression. "This opens up the idea that once we learn how the bacteria talk to the vagus, we may be able to simulate that with novel molecules – drugs without the bacteria," Bienenstock says.

Lyte, in a 2011 *BioEssays* paper, proposed a neurochemical "delivery system" by which gut bacteria, such as probiotics, can send messages to the brain. Gut bacteria both produce and respond to the same neurochemicals—such as GABA, serotonin, norepinephrine, dopamine, acetylcholine and melatonin—that the brain uses to regulate mood and cognition. Such neurochemicals probably allow the brain to tune its behavior to the feedback it receives from the army of bacteria in the gut. "And why not?" asks Lyte. After all, he says, considering the sheer abundance of bacteria awash in the human gut, "wouldn't it make sense that your brain would want to keep tabs on it?" Just how that communication unfolds is an open question, however. "We're really at the beginning of trying to understand how everything links up," Lyte says. What is clear already, he says, is that "it's a very interactive environment, much more so than we ever expected when we were trying to understand these things as stand-alone systems."

Programming brain development

Some research suggests that the gut microbiome's influence on behavior begins soon after birth, when microbes help "program" some aspects of brain development, such as its characteristic response to stress. In an influential 2004 study published in the *Journal of Physiology*, neuroimmunologist Nobuyuki Sudo, MD, of Kyushu University in Japan found that in germ-free mice, a brief period of confinement—a stressor commonly used in rodent experiments—triggered an exaggerated response from the hypothalamic-pituitary-adrenal (HPA) axis, the neuroendocrine network that governs the body's physiological response to stress. Specifically, the team found, stressed germ-free mice showed elevated levels of two hallmark stress hormones, corticosterone and adrenocorticotrophin.

It is possible to partly reverse this exaggerated stress response, Sudo's group found, but only within a brief window during early development. When the researchers transplanted fecal samples from mice with normal gut flora into the colons of germ-free infant mice, or even only one beneficial microbe, *Bifidobacterium infantis*, the mice later showed a normal HPA stress response. But if the fecal transplant was delayed until after the mice were weaned, the animals continued to have an exaggerated stress response.

Subsequent studies have provided further evidence that early exposure to normal gut bacteria is important for brain development and behavior. In a 2011 study published in *Proceedings of the National Academy of Sciences*, neuroscientist Rochellys Diaz Heijtz, PhD, of the Karolinska Institute in Sweden, and colleagues found that germ-free, unstressed mice were more active and more willing to explore exposed areas of a maze than mice that had normal gut microbiota. Like Sudo's group, Heijtz and her colleagues were able to erase those behavioral differences by transplanting normal gut bacteria into the germ-free mice, but only if they did so while the mice were babies—again suggesting that there is a critical window for gut bacteria to establish normal patterns of behavior in its host animal.

A two-way street

Just as gut bacteria affect the brain, the brain can also exert profound influences on the gut microbiome—with feedback effects on behavior. Numerous studies, for example, have shown that psychological stress suppresses beneficial bacteria. In a 2004 study in the *Journal of Pediatric Gastroenterology and Nutrition*, integrative immunologist Michael Bailey, now at Ohio State University, and colleagues at the University of Wisconsin–Madison found that infant monkeys whose mothers had been startled by loud noises during pregnancy had fewer *Lactobacilli and Bifidobacteria*. The results also extend to humans. In 2008, researchers led by psychologist Simon Knowles, PhD, of Swinburne University of Technology in Australia found that during exam week, university students' stool samples contained fewer lactobacilli than they had during the relatively untroubled first days of the semester.

In a 2011 study in mice that was published in *Brain, Behavior, and Immunity*, Bailey, Lyte and colleagues examined how such stress-induced changes to the gut microbiome affect health. They reported that sharing a cage with more aggressive mice—a "social disruption" stressor—tamped down beneficial bacteria, decreased the overall diversity of the gut microbiome, and promoted the overgrowth of harmful bacteria, making animals more susceptible to infection and causing inflammation in the gut.

In a follow-up study, Bailey and colleagues found that giving mice broad-spectrum antibiotics to suppress gut bacteria prevented stress from causing inflammation. Similarly, they found that germ-free mice also did not show stress-induced inflammation—but when the germ-free mice were colonized with a normal population of bacteria, stress again prompted gut inflammation.

"With all those experiments, we're really confident that these intestinal bacteria are playing a role in stress-induced increases in inflammation," Bailey says.

Stress-induced changes to the microbiome may in turn affect the brain and behavior. A few studies suggest that defensive molecules the gut produced during infection, called inflammatory cytokines, disrupt brain neurochemistry and make people more vulnerable to anxiety and depression. Bercik believes that process may help explain why more than half of people with chronic GI disorders such as Crohn's disease, ulcerative colitis and irritable bowel syndrome (IBS) are also plagued by anxiety and depression.

Recognizing that communication between the brain and the gut is bidirectional also points toward new ways of treating both the physical symptoms of intestinal disease and the psychological disorders that are so often present. Keeping anxiety and depression under control, Bercik suggests, may improve inflammation in the gut; and treating inflammation in the gut may improve mood by altering brain biochemistry.

But before clinicians can capitalize on gut bacteria to treat either physiological or psychological disorders, a great deal more research is needed. Despite intense interest in how beneficial gut bacteria might promote psychological well-being, few studies have probed such effects in human subjects. In one such study, published in the *British Journal of Nutrition* in 2011, researchers found that a 30-day course of probiotic bacteria (a mix of *Lactobacillus helveticus and Bifidobacteria longum*) led to decreased anxiety and depression in healthy human volunteers.

In an effort to better understand how gut bacteria affect human brain activity, Mayer and his collaborator, UCLA gastroenterologist Kirsten Tillsch, MD, have just completed a neuroimaging study examining the effects of probiotics on brain activity in healthy human volunteers. Mayer declines to detail the study's results since it is not yet published, but says the results revealed an "observable" effect on volunteers' brain activities while they viewed either neutral or negative emotional stimuli.

For his part, Bercik and his collaborators have set out to learn whether and how gut bacteria influence mood and brain function in IBS patients who also have depression and anxiety. They are now enrolling patients in an exploratory study that will examine the effect of the probiotic *Bifidobacterium longum* on a variety of measures, including mood, brain function and brain biochemistry. They hope to have results by the end of this year.

The days of analyzing a patient's gut bacteria to treat her depression or anxiety are probably far away. Still, scientists following this line of research have become increasingly convinced that to fully understand our emotions and behaviors, we need to study the gut as much as the brain.
