# Chemicals released by bacteria may help gut control the brain, mouse study suggests



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Gut microbes affect the function of nerve cells important for overcoming fear responses.

Christopher Parkhurst and David Artis (WCM)

The more researchers look, the more connections they find between the microbes in our intestines and those in our brain. Gut bacteria appear to influence everything from depression to autism. Now, a study on how mice overcome fear is starting to reveal more about the mysterious link between gut and mind.

“This work is amazing,” says Peng Zheng, a neuroscientist at Chongqing Medical University in China who was not involved with the research. The study, he says, could provide new insight into several mental disorders.

The research used a classic Pavlovian test: Shock a mouse on the foot while playing a tone and the rodent will quickly learn to associate the noise with pain, flinching whenever it hears the sound. But the association doesn’t last forever. After several sessions of hearing the tone but not getting the shock, the mouse will forget the association, and the sound will have no effect. This “forgetting” is important for people as well; it’s impaired, for example, in those with chronic anxiety and post-traumatic stress disorder.

David Artis, an immunologist and microbiologist at Weill Cornell Medicine in New York City, wondered whether gut bacteria played any role in the learning and forgetting responses. He and colleagues treated mice with antibiotics to totally rid them of the bacteria in their gut, collectively known as the microbiome. They then played a tone and right after gave the mouse a mild shock, doing this multiple times.

All of the animals quickly learned to associate the noise with pain, freezing when they heard the sound. But only mice with normal microbiomes eventually forgot the connection: By 3 days, the noise no longer affected them most of them, whereas the antibiotic-treated mice still reacted, the team reports today in *Nature*.

In another set of experiments, the scientists looked at the dissected brains of the mice and studied the gene activity and shape of individual brain cells. They discovered that a region of the brain known as the medial prefrontal cortex was involved in the differences between the treated and untreated mice. Some of the region's so-called excitatory neurons, which are involved in learning and memory, appeared to be key. When gut microbes were missing, these neurons failed to appropriately form and absorb spines that stick out of these cells, which help with learning and forgetting, the researchers report.

In addition, the team identified substantial changes in the amounts of four chemicals produced by the gut microbes that may help keep the fear-forgetting part of the brain in shape. The mice with no microbiome made much less of these chemicals. Two of the four chemicals are associated with neuropsychiatric diseases such as schizophrenia and autism, suggesting this brain-microbe connection may be involved in these diseases, Artis says.

The next step, adds Zheng, would be to prove these four microbial chemicals are causing the changes in the mouse brains. And it would also be helpful to wipe out specific microbes to pin down which microbial species are involved, says John Cryan, a neuroscientist at University College Cork in Ireland.

Regardless, "This paper is spearheading where the field should go," says Sven Pettersson, an experimental biologist at the Karolinska Institute in Stockholm. There is great interest in gut-brain connections, he explains, and too few studies that get at how they work. "The publication is helpful to a field full of phenomenology and overexcitement."