Gut microbes can boost the motivation to exercise, research finds

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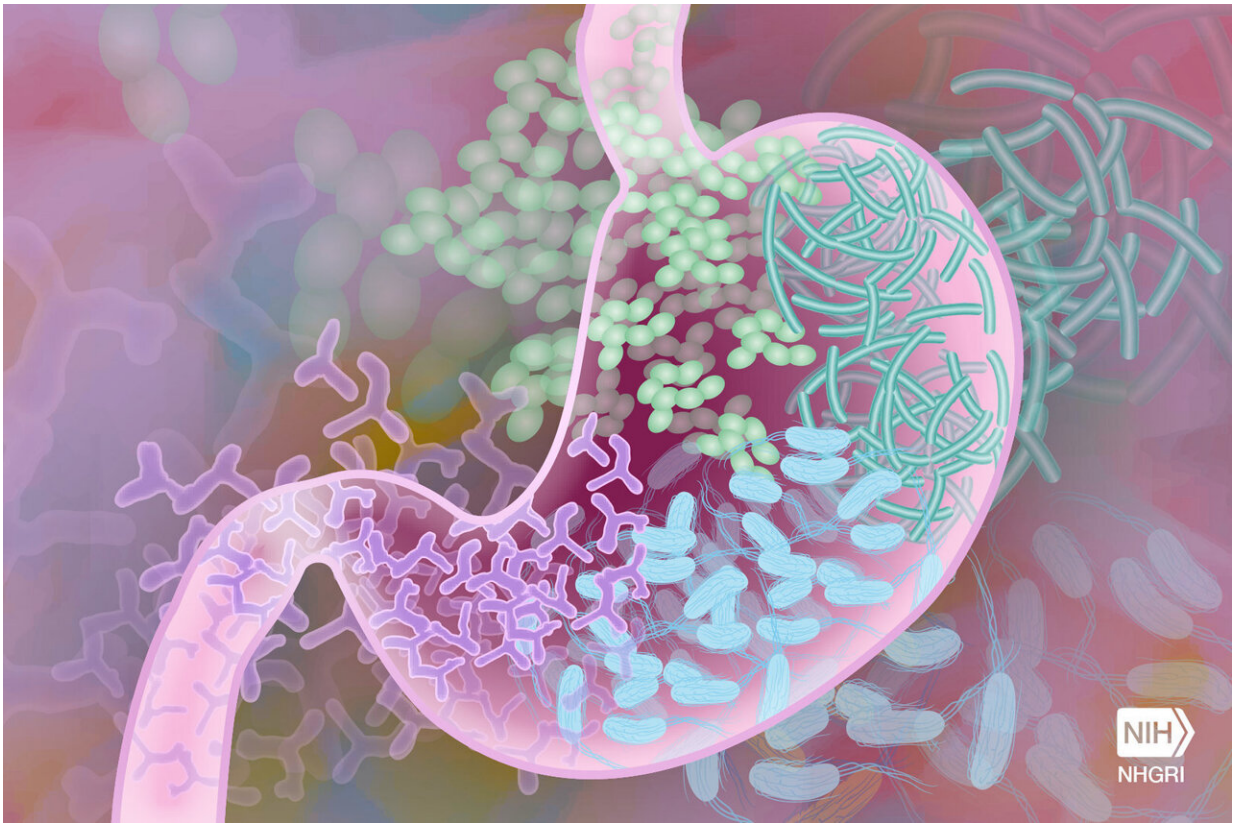

Illustration of bacteria in the human gut. Credit: Darryl Leja, National Human Genome Research Institute, National Institutes of Health

Some species of gut-dwelling bacteria activate nerves in the gut to promote the desire to exercise, according to a study in mice that was led

by researchers at the Perelman School of Medicine at the University of Pennsylvania. The study was published today in *Nature*, and reveals the gut-to-brain pathway that explains why some bacteria boost exercise performance.

In the study, the researchers found that differences in running performance within a large group of lab mice were largely attributable to the presence of certain gut bacterial species in the higher-performing animals. The researchers traced this effect to small molecules called metabolites that the bacteria produce—metabolites that stimulate sensory nerves in the gut to enhance activity in a motivation-controlling brain region during exercise.

"If we can confirm the presence of a similar pathway in humans, it could offer an effective way to boost people's levels of exercise to improve public health generally," said study senior author Christoph Thaiss, Ph.D., an assistant professor of Microbiology at Penn Medicine.

Thaiss and colleagues set up the study to search broadly for factors that determine exercise performance. They recorded the genome sequences, gut bacterial species, bloodstream metabolites, and other data for genetically diverse mice. They then measured the amount of daily voluntary wheel running the animals did, as well as their endurance.

The researchers analyzed these data using machine learning, seeking attributes of the mice that could best explain the animals' sizeable inter-individual differences in running performance. They were surprised to find that genetics seemed to account for only a small portion of these performance differences—whereas differences in gut bacterial populations appeared to be substantially more important. In fact, they observed that giving mice broad-spectrum antibiotics to get rid of their gut bacteria reduced the mice's running performance by about half.

Ultimately, in a years-long process of scientific detective work involving more than a dozen separate laboratories at Penn and elsewhere, the researchers found that two bacterial species closely tied to better performance, *Eubacterium rectale* and *Coprococcus eutactus,* produce metabolites known as fatty acid amides (FAAs). The latter stimulate receptors called CB1 endocannabinoid receptors on gut-embedded sensory nerves, which connect to the brain via the spine. The stimulation of these CB1 receptor-studded nerves causes an increase in levels of the neurotransmitter dopamine during exercise, in a brain region called the ventral striatum.

The striatum is a critical node in the brain's reward and motivation network. The researchers concluded that the extra dopamine in this region during exercise boosts performance by reinforcing the *desire* to exercise.

"This gut-to-brain motivation pathway might have evolved to connect nutrient availability and the state of the gut bacterial population to the readiness to engage in prolonged physical activity," said study co-author, J. Nicholas Betley, Ph.D., an associate professor of Biology at the University of Pennsylvania's School of Arts and Sciences. "This line of research could develop into a whole new branch of exercise physiology."

The findings open up many new avenues of scientific investigation. For example, there was evidence from the experiments that the better-performing mice experienced a more intense "runner's high"—measured in this case by a reduction in pain sensitivity—hinting that this well-known phenomenon is also at least partly controlled by gut bacteria. The team now plans further studies to confirm the existence of this gut-to-brain pathway in humans.

Apart from possibly offering cheap, safe, diet-based ways of getting ordinary people running and optimizing elite athletes' performance, he

added, the exploration of this pathway might also yield easier methods for modifying motivation and mood in settings such as addiction and depression.

The study was led by Penn Medicine scientist Lenka Dohnalová. Other Penn Medicine authors include: Patrick Lundgren, Jamie Carty, Nitsan Goldstein, Lev Litichevskiy, Hélène Descamps, Karthikeyani Chellappa, Ana Glassman, Susanne Kessler, Jihee Kim, Timothy Cox, Oxana Dmitrieva-Posocco, Andrea Wong, Erik Allman, Soumita Ghosh, Nitika Sharma, Kasturi Sengupta, Mark Sellmyer, Garret FitzGerald, Andrew Patterson, Joseph Baur, Amber Alhadeff, and Maayan Levy.

More information: A microbiome-dependent neuronal pathway regulates the motivation for exercise in mice, *Nature* (2022). doi.org/10.1038/s41586-022-05525-z

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