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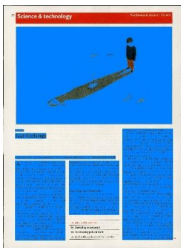

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Autism

Gut feelings

Experiments on intestinal bacteria may point the way to a treatment for autism

AUTISM AFFECTS people's social behaviour and communication, and may impair their ability to learn things. All this is well known. Less familiar to most, though, are the gastrointestinal problems associated with the condition. The intestines of children with autism often harbour bacteria different from those in the guts of the neurotypical. As a consequence, such people are more than three times as likely as others are to develop serious alimentary-canal disorders at some point in their lives.

Unfortunate though this is, the upset gut floras of autistic people are seen by some investigators as the key to the condition—and to treating it. Recent research has shown that altering animals' intestinal bacteria can have dramatic effects on their nervous systems. Ameliorating autism by tinkering with the ecology of the gut might thus be a fruitful line of inquiry.

A study just published in *Neuron* suggests that it is. In it, Mauro Costa-Mattioli of Baylor College of Medicine, in Texas, and his colleagues demonstrate that introducing a particular bacterium into the guts of mice that display autistic symptoms can abolish some of those symptoms. The bug in question is *Lactobacillus reuteri*. It is commonly found in healthy digestive systems and helps regulate acidity levels. And it is also easily obtainable for use as a probiotic from health-food shops.

Mens sana in corpore sano

Dr Costa-Mattioli and his team first reported *L. reuteri*'s effects on autism in 2016, after conducting experiments with obese female mice. These animals have a tendency to give birth to offspring with autistic traits familiar from people—unwillingness to socialise, repetitive behaviour and unwillingness to communicate (in the case of mice, via ultrasonic squeaking). The researchers noted that the guts of both the obese mothers and their young were bereft of *L. reuteri*. They wondered what effect transplanting these bugs into the animals might have. They found, when they did so to the offspring, that the youngsters' autism-like traits vanished.

That led to the latest experiments, on mice that have autistic symptoms induced in four other, different ways. Some were genetically edited to be autistic. Some were exposed to valproic acid, a drug used to

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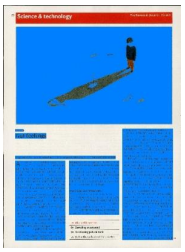

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treat bipolar disorder and migraines that is known to induce autism in fetuses. Some had their guts cleared of all bacteria. And some belonged to a strain called BTBR, individuals of which display autism-like traits that have no known cause.

Martina Sgritta, one of Dr Costa-Mattioli's colleagues, analysed the bacteria in the guts of all of these animals. She found that, while the genetically engineered mice and the BTBR mice had, as expected, reduced levels of *L. reuteri*, and those with bacteria-free guts were (obviously) free of the bug altogether, the valproic-acid mice had normal amounts of the bacterium.

This last result was unexpected, but the team carried on regardless. They arranged for between seven and 15 mice of each of the four types to have, starting at the age of three weeks, their drinking water laced with *L. reuteri*. Equivalent numbers of each type continued to be given ordinary water as a control. During the course of the experiment the mice had their faeces collected regularly, so that their bacteria could be tracked. And, at the age of seven weeks, they were given two sorts of social tests.

The first test involved putting each experimental mouse into a perspex container from which it could go either into a chamber where there was an empty wire cup or into one where there was a similar cup containing an unfamiliar mouse. Subject mice were left in the container for ten minutes and were monitored to see how long they spent with the empty cup and with the other mouse.

The second test placed a mouse in an arena where another, unfamiliar mouse was already present. An observer, who did not know which mice were controls and which had been given *L. reuteri* in their water, then noted how often over the course of ten minutes the two mice touched, sniffed, groomed and crawled on one another.

In both tests, all the mice that had had their water laced with *L. reuteri*, regardless of how their autism had been induced, were more sociable than equivalents that had been drinking unlaced water. In the first, they spent twice as much time with the mouse under the wire cup. In the second, they engaged in many more social interactions with the unfamiliar mouse.

The team's initial hypothesis had been that the supplementary *L. reuteri* were somehow changing the gut flora of the mice exposed to them into something more normal. But they weren't. Indeed, *L. reuteri* proved able to abolish autistic behaviour even in those mice which had guts otherwise devoid of microbes—as well as in those with valproic-acid-induced autism, which already had normal levels of the bug. That suggests boosting levels of this bacterial species is shaping behaviour all by itself.

Their next hypothesis was that the bacterium was doing this by interacting somehow with oxytocin, a hormone that shapes behaviour and plays a part in the ways in which people and other mammals form social bonds. Dr Costa-Mattioli knew from work published in 2013 that spraying oxytocin into the noses of mice with autistic symptoms helps to ameliorate some of those symptoms. Dr Sgritta therefore ran the experiments again, but this time on autistic mice that had had the oxytocin receptors on the relevant neurons disabled by genetic engineering. In these new experiments, the presence of *L. reuteri* in drinking water had no effect.

Follow-up examinations of the mice in all these experiments looked at the strengths of connections between nerve cells within part of the brain called the ventral tegmental region. This region regulates, among other things, motivation and reward-related social behaviour. Nerve signals are carried by the movement of ions (electrically charged atoms), so the team were able to measure connection-strength by monitoring the flow of ions at the junctions between nerve cells in this region. Strong connections, with lots of ion flow, indicated that social experiences were rewarding. These were normal in the mice exposed to *L. reuteri*, which makes sense since animals treated with the bacterium sought out more social experiences. Conversely, weak connections (those with little ion flow) indicated that social experiences were not triggering a reward. Such weak connections were found in animals that had not been exposed to the bacterium.

The researchers suspected that such effects were controlled by signals from the gut that are being transmitted by the vagus nerve, which connects gut and brain. To test this idea they cut that nerve in selected animals. In these animals, subsequent treatment with *L. reuteri* failed to abolish their autistic symptoms.

The crucial aspect of this work is *L. reuteri*'s wide availability—an availability approved by regulators such as America's Food and Drug Administration. This existing approval, which means *L. reuteri* poses no known health hazard, simplifies the process of organising clinical trials.

Clearly, autism in people is more complicated than a mere willingness to associate with others. And getting too excited about a mouse trial is usually a mistake. But in Dr Costa-Mattioli's view his results, which have been replicated in part by Evan Elliot's laboratory in Bar-Ilan University, Israel, would justify embarking on at least preliminary trials intended to determine whether *L. reuteri* has positive effects on people with autism, and might thus be worth pursuing.

Others agree. Sarkis Mazmanian of the California Institute of Technology works in the same area. He says of these results: "I think the bar is now very low for getting this research moved on to human trials since most people already have these bacteria inside them and we know there are few, if any, safety or toxicity issues."

The general availability of *L. reuteri* does, however, bring with it another possibility—that people will conduct their own, "off label" trials, either on themselves or on their children. Dr Mazmanian is cautious about that idea. "I don't know if there is a barrier to people buying and using this stuff now. It may be strain-specific and the paper does not state which strain or strains were used," he says.

At the moment, Dr Costa-Mattioli is unwilling to divulge that information. He is expecting to publish another paper soon, though, with more details. In practice, it may be hard to discourage people from testing *L. reuteri*'s effects themselves. All the more reason to do properly conducted trials quickly. ■

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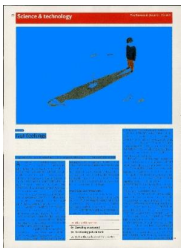

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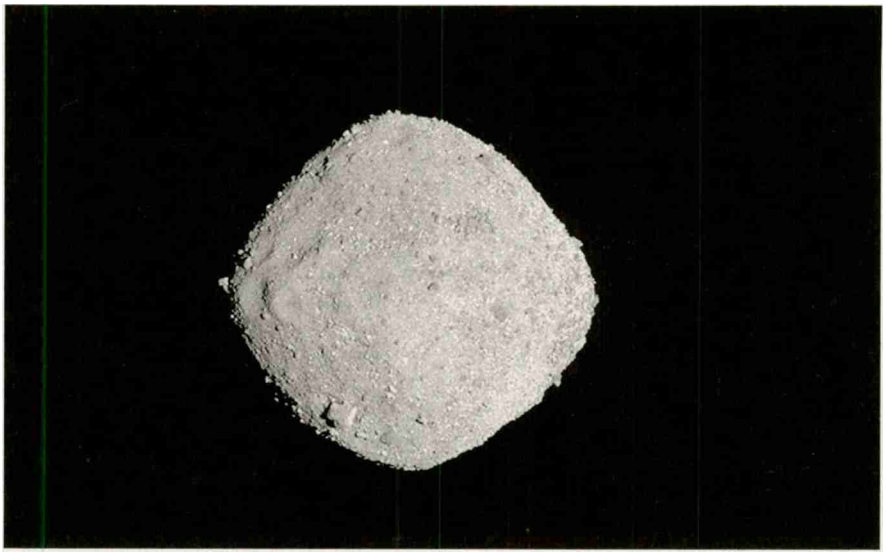

Hello to Bennu

Another stamp has just been added to the album of objects in the solar system visited by space probes. Bennu, pictured, is an asteroid that orbits the sun at approximately the same distance as Earth. This proximity, plus spectral analysis of its chemical composition (carbon-rich), radar analysis of its surface (smooth) and telescopic analysis of its spin rate (slow), made it the target of choice for a sample-return mission. That mission, OSIRIS-Rex, arrived on December 3rd. After an extensive inspection from an altitude of a few kilometres, OSIRIS-Rex will, in July 2020, swoop down and grab about 60 grams of material from the surface. It will leave Bennu in March 2021 and deliver the sample to Earth, in a special landing capsule, in September 2023.