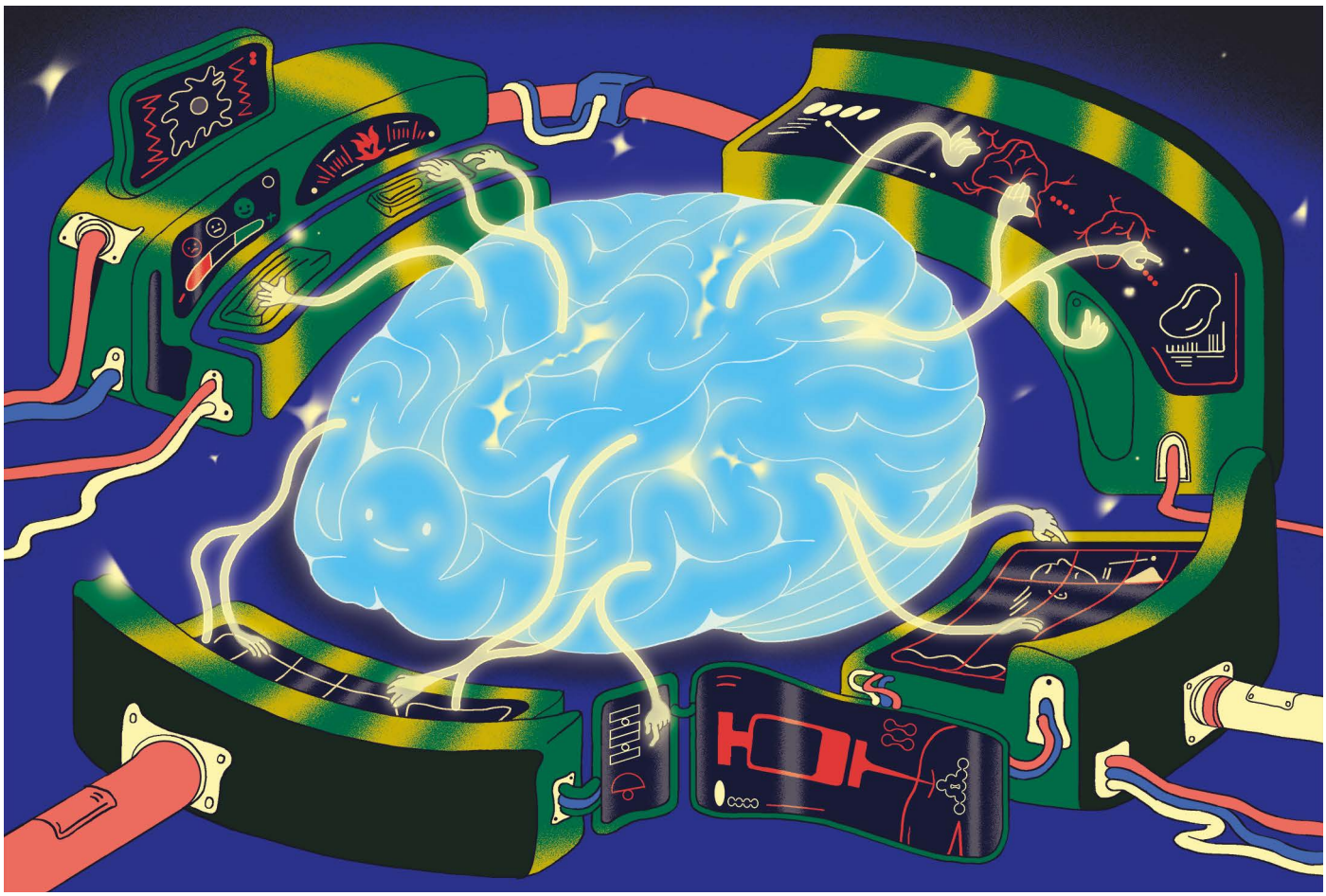


ILLUSTRATION BY DALBERT B. VILARINO

HOW THE BRAIN CONTROLS SICKNESS AND HEALTH

Scientists hope that deciphering the connections between the brain and the immune system will help to treat a range of diseases. **By Diana Kwon**

Hundreds of scientists around the world are looking for ways to treat heart attacks. But few started where Hedva Haykin has: in the brain.

Haykin, a doctoral student at the Technion – Israel Institute of Technology in Haifa, wants to know whether stimulating a region of the brain involved in positive emotion and motivation can influence how the heart heals.

Late last year, in a small, windowless microscope room, she pulled out slides from a thin black box, one by one. On them were slices of hearts, no bigger than pumpkin seeds, from mice that had experienced heart attacks. Under a microscope, some of the samples were clearly marred by scars left in the aftermath of the infarction. Others showed mere speckles of damage visible among streaks of healthy, red-stained cells.

The difference in the hearts' appearance originated in the brain, Haykin explains. The healthier-looking samples came from mice that had received stimulation of a brain area involved in positive emotion and motivation. Those marked with scars were from unstimulated mice.

"In the beginning we were sure that it was too good to be true," Haykin says. It was only after repeating the experiment several times, she adds, that she was able to accept that the effect she was seeing was real.

Haykin, alongside her supervisors at the Technion – Asya Rolls, a neuroimmunologist, and Lior Gepstein, a cardiologist – are trying to work out exactly how this happens. On the basis of their experiments so far, which have not yet been published, activation of this brain reward centre – called the ventral tegmental area (VTA) – seems to trigger immune changes that contribute to the reduction of scar tissue.

This study has its roots in decades of research pointing to the contribution of a person's psychological state to their heart health[1]. In a well-known condition known as 'broken-heart syndrome', an extremely stressful event can generate the symptoms of a heart attack – and can, in rare cases, be

fatal. Conversely, studies have suggested that a positive mindset can lead to better outcomes in those with cardiovascular disease. But the mechanisms behind these links remain elusive.

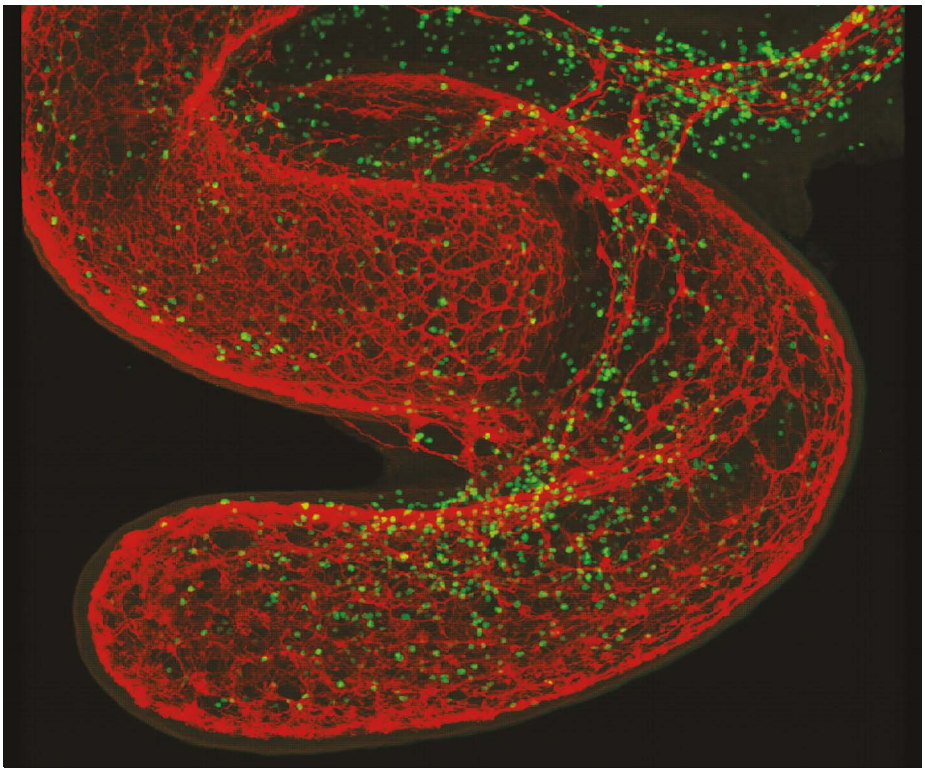
Rolls is used to being surprised by the results in her laboratory, where the main focus is on how the brain directs the immune response, and how this connection influences health and disease. Although Rolls can barely contain her excitement as she discusses her group's eclectic mix of ongoing studies, she's also cautious. Because of the often-unexpected nature of her team's discoveries, she never lets herself believe an experiment's results until they have been repeated multiple times – a policy that Haykin and others in her group have adopted. "You need to convince yourself all the time with this stuff," Rolls says.

For Rolls, the implications of this work are broad. She wants to provide an explanation for a phenomenon that many clinicians and researchers are aware of: mental states can have a profound impact on how ill we get – and how well we recover. In Rolls's view, working out how this happens could enable physicians to tap into the power of the mind over the body. Understanding this could help to boost the placebo effect, destroy cancers, enhance responses to vaccination and even re-evaluate illnesses that, for centuries, have been dismissed as being psychologically driven, she says. "I think we're ready to say that psychosomatic [conditions] can be treated differently."

She is part of a growing group of scientists who are mapping out the brain's control over the body's immune responses. There are multiple lines of communication between the nervous and the immune systems – from small local circuits in organs such as the skin, to longer-range routes beginning in the brain – with roles in a wide range of diseases, from autoimmunity to cancer. This field "has really exploded over the last several years", says Filip Swirski, an immunologist at the Icahn School of Medicine at Mount Sinai in New York City.

Some parts of the system – such as the vagus nerve, a huge highway of nerve fibres that connects the body to the brain – have inspired treatments for several autoimmune diseases that are currently being tested in clinical trials. Other studies, investigating how to recruit the brain itself – which some think could provide powerful therapies – are still nascent. Rolls, for one, has just begun examining whether the pathways her team has found in mice are also present in humans. And she has launched a start-up company to try to develop treatments based on her findings.

Although these developments are encouraging to researchers, much is still a mystery. "We often have a black box between the brain and the effect we see in the periphery," says Henrique Veiga-Fernandes, a neuroimmunologist at the Champalimaud Centre for the Unknown in Lisbon. "If we want to use it in the therapeutic context, we actually need to understand the mechanism."



LARA SANTOS/VEIGA-FERNANDES LAB

Neuronal cells (red) in the gut interface with cells of the immune system (green).

A tale of two systems

For more than a century, scientists have been finding hints of a close-knit relationship between the nervous and the immune systems. In the late nineteenth and early twentieth centuries, for example, scientists demonstrated that cutting nerves to the skin could curb some hallmarks of inflammation[2].

It wasn't until the late 1990s that researchers in this field began drawing connections to the body's master conductor, the brain. Neurosurgeon Kevin Tracey, then at North Shore University Hospital in Manhasset, New York, and his colleagues found something unexpected while investigating whether an experimental anti-inflammatory drug could help to tame brain inflammation caused by stroke.

When delivered into the brains of rodents that had experienced strokes, the drug had the expected effect: it reduced neuroinflammation. As a control, the team injected the drug into the brains of animals that had inflammation throughout their bodies, thinking the drug would work exclusively in the brain. To their surprise, it also worked in the body. "This was a real head-scratcher," says Tracey, now president and chief executive of the Feinstein Institutes for Medical Research in Manhasset.

After months of trying to determine the path of the drug from brain to body, the researchers decided to cut the vagus nerve, a bundle of some 100,000 nerve fibres that runs from the brain to the heart, lungs, gastrointestinal tract and other major organs. With the vagus nerve snipped, the anti-inflammatory effect of the brain-administered drug disappeared[3].

Inspired by this discovery, Tracey's group and others have continued to explore other ways in which the vagus nerve – and the rest of the nervous system – directs immune responses. A driving force for these developments, says Swirski, has been the advent of scientific tools that enable scientists to begin to chart the interactions between the nervous and the immune systems in an unprecedented way.

Some researchers are focusing on particular body systems. For instance, a team led by Andreas Habenicht, a cardiologist at LMU Munich, Germany, reported last year that the interaction between immune cells and nerves in the outermost layer of artery walls modulated the progression of atherosclerosis, an inflammatory disease in which vessels become clogged with cholesterol and other substances[4].

Meanwhile, Veiga-Fernandes and his group have documented clusters of neuronal and immune cells in various tissues and discovered how they work together to sense damage and mobilize immune reactions. His team is now looking at how these little switchboards can be controlled by the brain[5].

The brain itself is also beginning to give up its secrets. Neuroscientist Catherine Dulac and her team at Harvard University in Cambridge, Massachusetts, have pinpointed neurons in an area called the hypothalamus that control symptoms including fever, warmth-seeking

and loss of appetite in response to infection[6]. "Most people probably assume that when you feel sick, it's because the bacteria or viruses are messing up your body," she says. But her team demonstrated that activating these neurons could generate symptoms of sickness even in the absence of a pathogen. An open question, Dulac adds, is whether these hypothalamic neurons can be activated by triggers other than pathogens, such as chronic inflammation.

Just above the hypothalamus sits a region called the insula, which is involved in processing emotion and bodily sensations. In a 2021 study, one of Rolls's doctoral students, Tamar Koren, found that neurons in the insula store memories of past bouts of gut inflammation — and that stimulating those brain cells reactivated the immune response[7].

Rolls, Koren and their colleagues suspect that such a reaction might prime the body to fight potential threats. But these reactions could also backfire and start up in the absence of the original trigger. This could be the case for certain conditions, such as irritable bowel syndrome, that can be exacerbated by negative psychological states.

Mind over matter

Many scientists hope to pin down how such mental states influence immune responses.

Rolls and Fahed Hakim, a paediatrician and director of the Nazareth Hospital EMMS in Israel, were inspired to investigate this question after coming across a 1989 study[8] reporting that, among women with breast cancer, those who underwent supportive group therapy and self-hypnosis in addition to routine cancer care survived longer than those who received only the latter. Several other studies have documented a similar link between survival and the mental states of people with cancer.

To test the link, Rolls, Hakim and their team zoomed in on the VTA — the same region they targeted in the heart-attack study and in a previous experiment looking at bacterial infection. This time they focused on mice with lung and skin tumours. Activating neurons in the VTA noticeably shrank the cancers[9]. It turned out that VTA activation subdued cells in the bone marrow that would usually repress immune activity, freeing the immune system to fight the cancer.

Clinicians have known about the effect of positive thinking on disease progression for a long time, Hakim says. But this evidence has been largely anecdotal or correlational, so being able to identify a pathway through which such an effect occurs — and manipulate it experimentally in animals — makes it much more real, he says.

Negative mental states can also influence the body's immune response. In a study published last year, Swirski and his team identified specific brain circuits that mobilize immune cells in the bodies of mice during acute stress[10]. The researchers found two pathways, one originating in the motor cortex that directed immune cells to the site of injury or infection, and another beginning in the hypothalamus — a key responder in times of stress — that reduced the number of immune cells circulating in the blood. The group is now investigating the role of stress-mediated circuits in chronic inflammatory diseases.

Neuroscientist Jeremy Borniger at Cold Spring Harbor Laboratory in New York and his colleagues have also found that activating neurons in the mouse hypothalamus can generate an immune response[11] — and are now examining how manipulating these cells can alter the growth of tumours.

Some groups are hoping to replicate their findings in humans. Swirski's team, for instance, plans to use tools such as virtual reality to manipulate people's stress levels and see how that changes the immune response.

Koren and Rolls are working with Talma Hendler, a neuroscientist and psychiatrist at Tel Aviv University in Israel, to see whether boosting the reward system in people's brains before they receive a vaccine can improve their immune response. Rather than stimulating the brain directly, they are using a method called neurofeedback, in which individuals learn to observe and control their own brain activity; this is measured using methods such as functional magnetic resonance imaging.

> "YOU NEED TO CONVINCE YOURSELF ALL THE TIME WITH THIS STUFF."

The road to the clinic

Over the years, Rolls would chat with her good friend Tehila Ben-Moshe about her research. Ben-Moshe is the chief executive of Biond Biologics, an Israel-based biopharmaceutical company that focuses on using immune cells to target cancer. During one such discussion last year, Ben-Moshe realized that Rolls's brain-stimulation experiments were acting on some of the same immune cells that her company was trying to target, and immediately saw the therapeutic potential. "When I saw Asya's data, I couldn't believe what I saw," says Ben-Moshe. "The question then became — how can I translate what she's doing with mice into patients?" The two are working on launching a company.

Ben-Moshe and Rolls hope to harness existing brain-stimulation technologies, such as transcranial magnetic stimulation, which uses magnetic pulses to alter brain activity, or focused ultrasound, which uses sound waves, to modulate the immune systems of people with cancer, autoimmune diseases or other conditions. As a first step, their team has been reaching out to companies that have developed such technologies. Before starting clinical trials, Ben-Moshe and Rolls want to examine blood samples from trials already performed with these techniques, to see whether there are signs of immune-system alterations before and after treatment.

Potential therapies targeting the vagus nerve are nearer the clinic. A company co-founded by Tracey — SetPoint Medical in Valencia, California — is testing pill-sized vagus-nerve stimulators, implanted in the vagus nerve in the neck, in autoimmune diseases including Crohn's disease, multiple sclerosis and rheumatoid arthritis. The rheumatoid-arthritis trial is farthest along — the team has shown in a small trial in Europe that its device can reduce disease severity[12]. The technique is currently undergoing a randomized, sham-controlled trial (in which the control group will receive an implant but no active stimulation) in 250 patients in various centres across the United States.

Rolls's hope is that this work will ultimately help physicians to understand, and act on, the mind–body connections that they see in their practices. The need is clear: when Rolls put out a call to speak to psychologists from the hospital where her lab is based, the meeting room was packed. People from departments ranging from dermatology to oncology were eager to share their stories. Many clinicians pass people with seemingly psychosomatic issues on to psychologists, saying there is nothing physically wrong, said one attendee. This can be distressing for the person seeking treatment. Even being able to simply tell people that there is a brain–immune connection that is responsible for their symptoms can make an enormous difference.

It's time that both researchers and clinicians take the link between psychology and physiology seriously, says Rolls. "You can call something psychosomatic, but in the end, it's somatic. How long can we ignore what is there?"

Diana Kwon is a journalist based in Berlin.

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