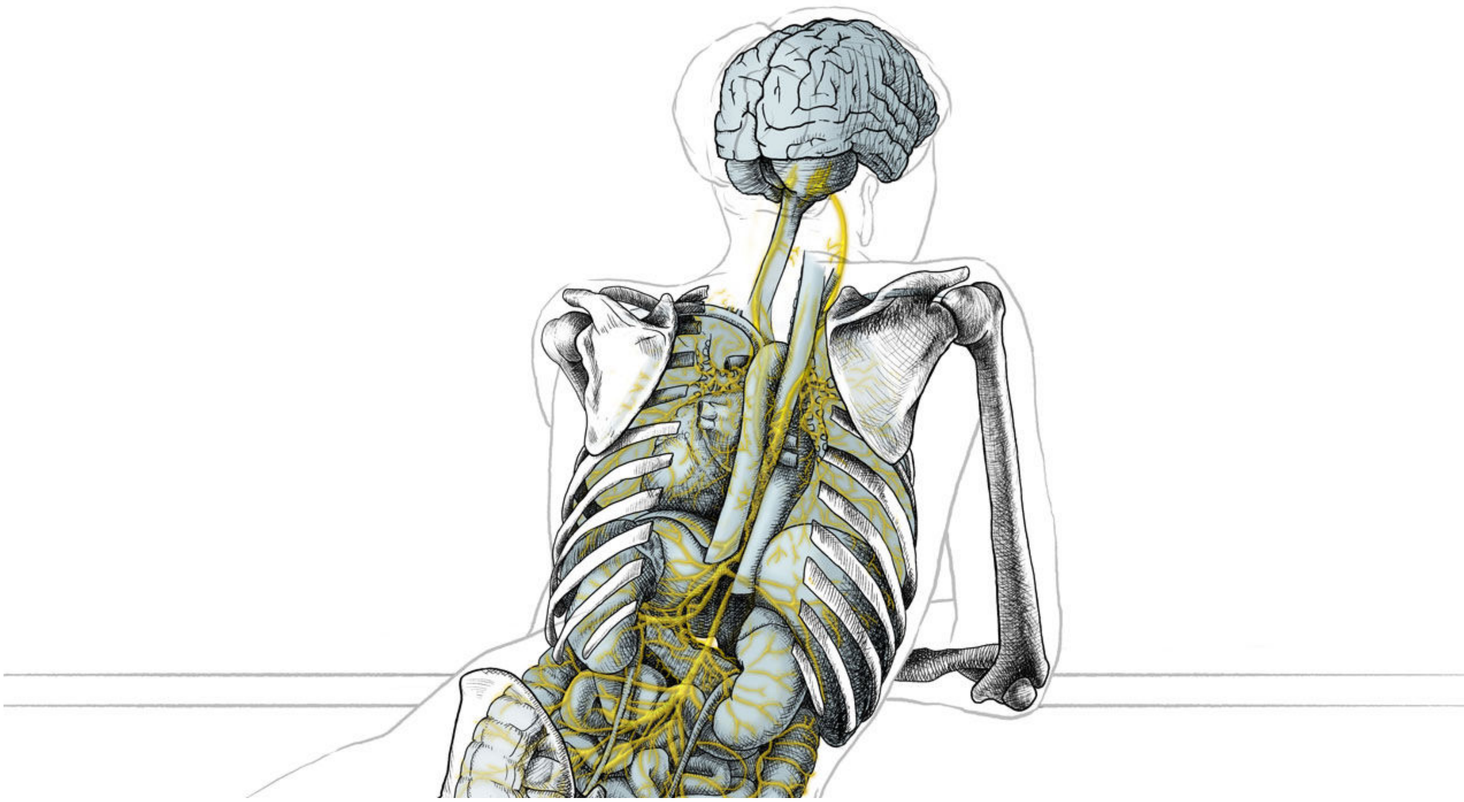


The vagus nerve forms a complex network linking the brain and internal organs. V. ALTOUNIAN/*SCIENCE*

Newly detailed nerve links between brain and other organs shape thoughts, memories, and feelings

By **Emily Underwood** | Jun. 10, 2021 , 12:55 PM

In the 1930s, neurosurgeon Wilder Penfield pioneered a daring new kind of cartography. As a stenographer took notes, he delicately touched an electrode to the exposed brains of his awake, consenting patients and asked what they felt as electrical current hit different areas.

Penfield wanted to better predict which brain functions would be threatened when surgeons had to remove tumors or chunks of tissue that were triggering epileptic seizures. Stimulating adjacent brain regions, he found, produced sensations in corresponding body parts: hand, forearm, elbow. The result of his mapping was the iconic “homunculus”: a map on the brain’s wrinkled outer layer representing the surface of the body.

Penfield then ventured into more mysterious territory. When he probed the insula, a deep fold of cortex, some patients felt nauseated or gassy; others belched or vomited. “My stomach is upset and

I smell something like medicine," one said.

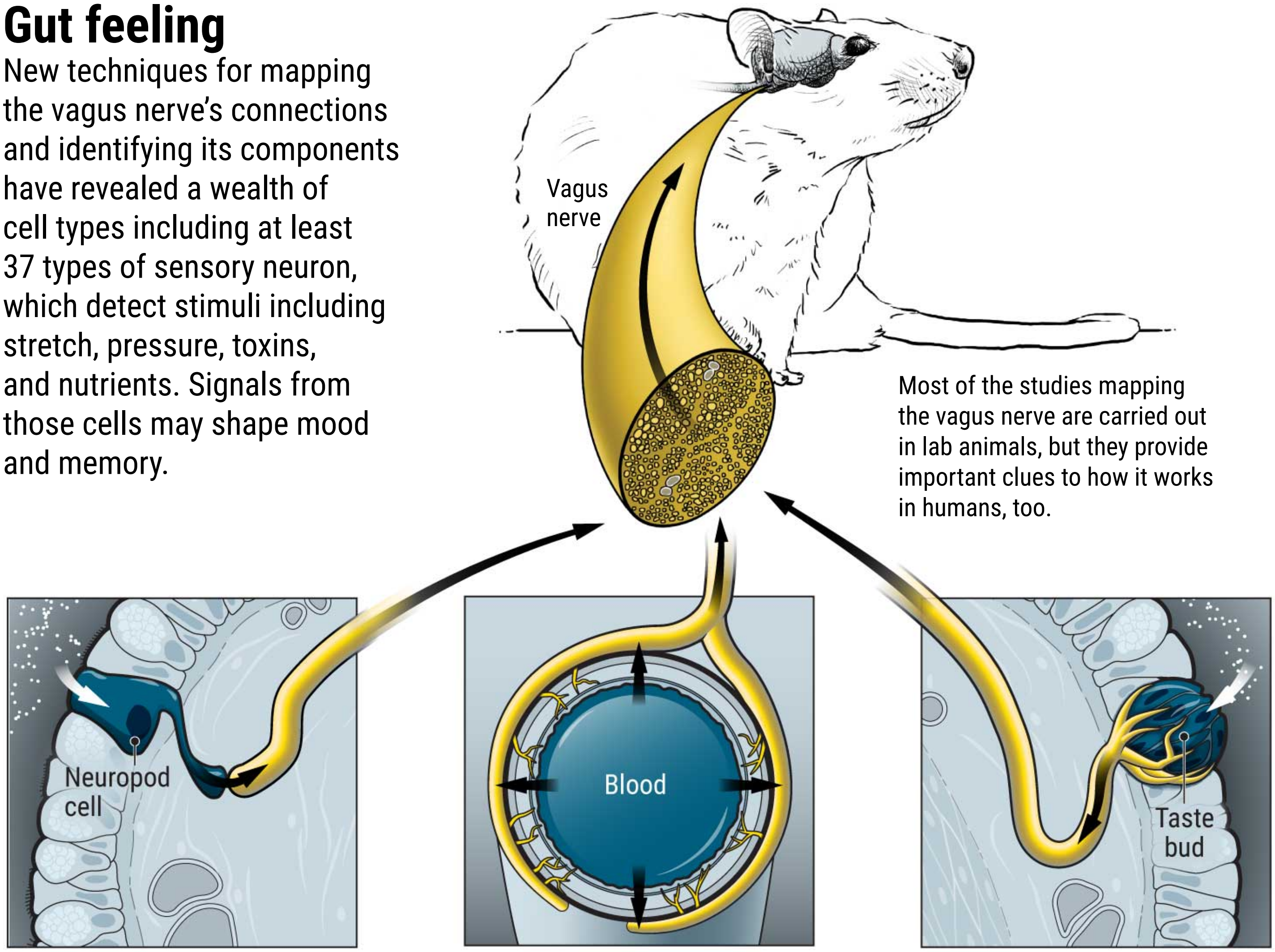
Penfield found those visceral signals harder to decipher than the brain's map of the body's surface. Brain regions responsible for different internal sensations seemed to overlap. Sensory regions were hard to distinguish from those that sent motor instructions such as telling the intestines to contract. Penfield once asked participants to swallow an electrode to detect changes in gut contractions while he stimulated their brains. But his map of the inner organs was blurry and ambiguous—and stayed that way for most of the next century.

Decades later, scientists are starting to unravel how our wet, spongy, slippery organs talk to the brain and how the brain talks back. That two-way communication, known as interoception, encompasses a complex, bodywide system of nerves and hormones. Much recent exploration has focused on the vagus nerve: a massive, meandering network of more than 100,000 fibers that travel from nearly every internal organ to the base of the brain and back again.

With new techniques for mapping the routes of nerves in animals and measuring interoception in people, researchers are adding surprising new details to the rough sketches Penfield and others devised. For more than 100 years, scientists have known that the vagus nerve carries signals between the organs and the brainstem. As part of the parasympathetic nervous system—active when the body is at ease or recovering from stress—the vagus regulates autonomic functions such as heart rate, breathing, and digestion. But new studies have shown signals carried by vagal fibers climb beyond the brainstem, revealing a broad interoceptive network in the brain that interprets internal changes, anticipates the body's needs, and sends commands to fulfill them. The network includes brain regions involved in more complex cognition, which means the nerves monitoring the body's basic workings also respond to—and influence—how we remember, process emotion, and even construct our sense of self.

Gut feeling

New techniques for mapping the vagus nerve's connections and identifying its components have revealed a wealth of cell types including at least 37 types of sensory neuron, which detect stimuli including stretch, pressure, toxins, and nutrients. Signals from those cells may shape mood and memory.



Intestine
Neuropod cells in the intestine sense nutrients such as glucose and send millisecond-quick signals through the vagus to the brain.

Vessels (aorta)
Clawlike vagal neurons that sense stretch in the aorta keep tabs on blood pressure.

Larynx
A group of roughly 100 neurons in the mouse larynx detects chemical irritants, defending the airway and triggering coughing.

V. ALTOUNIAN/*SCIENCE*

Challenging traditional distinctions between disorders of the brain and body, the new studies may hold clues to the nature of consciousness. Compared with better understood senses such as vision, interoception is like "a new continent," says Catherine Tallon-Baudry, a neuroscientist at the École Normale Supérieure.

The evidence that interoception holds keys to both physical and emotional wellbeing makes the vagus a tantalizing therapeutic target. Vagus nerve stimulation (VNS), which delivers pulses of electricity to the vagus through a device implanted under the collarbone, is already approved in the United States to treat epilepsy and depression. Less invasive forms of stimulation, including a device that delivers current to the skin of the neck and an ear-worn device called transcutaneous auricular VNS (taVNS), are under investigation for conditions as diverse as rheumatoid arthritis, obesity, and Alzheimer's. Yet how either approach might work and how to minimize side effects is unclear. Stimulating the vagus "clearly does many things to the body," says Kara Marshall, a postdoctoral fellow who studies interoception at Scripps Research. "The challenge is finding clear mechanisms."

TO DO THAT, researchers first need to map the vagus nerve's complex connections and then lay out how the brain represents and responds to its messages. That task is daunting because, as with many peripheral nerves, the vagus nerve has many thin, sparse fibers that lack an insulating layer of fatty myelin, making them notoriously hard to trace.

But new tools are sharpening the picture. Single-cell RNA sequencing, which allows scientists to identify cell types within a tissue on the basis of their patterns of gene expression, has at last made it possible to dissect the "dark matter of the vagus," says Steve Liberles, a cell biologist at Harvard Medical School. His team used genetics to identify a "staggering diversity" of vagal cell types in rodents, including cells that control breathing and trigger cough, sense changes in blood pressure and oxygen, and detect stretching and nutrients in the digestive system. Most recently, Liberles's team discovered cells in the brainstem, connected to vagal neurons, that trigger nausea. That finding could lead to more tolerable chemotherapies that avoid stimulating those nerve pathways or even tamp them down.

Researchers can also inject lab animals with a form of rabies virus that spreads through connected neurons from organs into the brain. Peter Strick, a neuroscientist at the University of Pittsburgh, injected the virus into rat stomachs and discovered vagal pathways that lead to the rostral insula, a poorly understood region thought to process sensations from internal organs and regulate emotions. Strick later showed that those insula cells stimulate digestion, whereas a second vagus tract extending from the motor cortex to the stomach does the opposite—arresting acid production and muscle contractions that help digest and move food.

The findings, published last year in the *Proceedings of the National Academy of Sciences*, might revive the notion that stress causes stomach ulcers. That idea was largely dismissed in the 1980s after a study that led to a 2005 Nobel Prize traced them to bacterial infections with *Helicobacter pylori*. But the new work suggests stress, by disrupting either vagal pathway, might hinder digestion and create a more welcoming environment for ulcer-inducing bacteria in the stomach, Strick says.

Other studies of vagus connections suggest they influence memory and learning. In a 2018 study in rats, neuroscientist Scott Kanoski at the University of Southern California severed sensory vagal connections between the stomach and the hippocampus, a brain region crucial to forming memories. The interruption prevented the animals from remembering new objects and locations and slowed the birth of neurons. Interoceptive signals help the hippocampus form life-sustaining memories: where we last found a really good snack, for example, or what meal made us sick.

Vagal circuits also drive motivation and mood, recent studies show. In 2018, neuroscientist Diego Bohórquez at Duke University discovered a direct vagal connection between nutrient-sensing cells in the mouse gut called neuropods and the brain. In a second study, neuroscientist Ivan de Araujo at the Icahn School of Medicine at Mount Sinai discovered that stimulating these circuits with a laser triggers the release of the rewarding neurotransmitter dopamine in the brain, motivating the rodents to seek more stimulation. The studies could help explain why eating feels good, and how stimulating the vagus in people alleviates depression.

Harvard University neuroscientist Vitaly Napadow (left) attaches a transcutaneous auricular vagus nerve stimulation device to the ear of his collaborator, Ronald Garcia. JEFFREY ANDREE/MASSACHUSETTS GENERAL HOSPITAL

A pressing question is how brain-body communications go awry. In 2019, Mount Sinai neuroscientist Paul Kenny discovered a startling link between nicotine addiction and type 2 diabetes in rats. When nicotine binds to neuronal receptors in a brain region called the habenula, Kenny found, it prompts the pancreas to release glucagon, a hormone that raises blood sugar. Over time, those signals can stress the pancreas, increasing diabetes risk. Meanwhile, chronically high glucose levels—communicated through the vagus and other interoceptive pathways—cause the habenula to respond less vigorously to nicotine, prompting the rats to seek more of the drug. That result suggests diabetes could make people more prone to nicotine addiction.

Before that study, “I didn’t consider anything south of the neck” when studying addiction, Kenny says. Now, those complex links between nicotine consumption, metabolic dysregulation, and addiction have led him to question whether addiction can really be considered purely a brain disorder.

Although some psychiatric disorders clearly originate in the brain alone, “I am convinced that in other cases [they] can originate in the body,” says neurosurgeon Kevin J. Tracey, president of the

Feinstein Institutes for Medical Research. His team has studied how signals between the brain and viscera modulate the immune system, and recently identified a cluster of cells in the mouse brainstem that regulates inflammation by sending signals through the vagus to the spleen.

Lisa Feldman Barrett, a neuroscientist at Northeastern University, points to evidence that mood disorders can stem from metabolic problems—which in turn can have roots in stressors that affect the brain, such as early childhood trauma and neglect or sleep deprivation. Such experiences can also shape how we interpret internal sensations. Rather than passively receiving information, the brain is constantly constructing a model of its sensory conditions and guessing what caused them in order to direct the correct response, Barrett says. “You feel a tug in your chest, and your brain has to decide if it’s because you ate too much for dinner or if it’s the early sign of a heart attack.”

STUDYING HOW HUMANS experience their internal sensations is tricky, however, as Penfield discovered. Many signals are unconscious, and when they do rise to our awareness, they’re often blurry and ambiguous, making it hard for people to report what they’re experiencing. If vision is like high-definition TV, “our awareness of interoception is like 1950s black-and-white television with bad reception in a rainstorm,” Barrett says.

Commonly used tests of interoceptive awareness ask people to detect or count their own heartbeats, an interoceptive signal transmitted by the vagus. But these tasks are hard to do at rest, and are easily biased by prior knowledge about heart rate from, say, wearing a fitness tracker. Other interoceptive tests are frightening or uncomfortable, such as taking an adrenalinelike drug that makes your heart pound or swallowing a balloon that inflates in your gastrointestinal tract. And perturbing vital processes such as heartbeat to test a person’s awareness of them can be invasive and risky, says neuroscientist Sahib Khalsa at the Laureate Institute for Brain Research: “You need ways to probe interoception safely.”

Khalsa is among those looking for minimally invasive measures. His team recently asked 40 healthy people to swallow a capsule that buzzes randomly as it moves through the stomach. Khalsa took a capsule himself and says it’s a bizarre sensation. “Imagine if you put your phone on vibrate and swallowed it, and then someone started calling you.”

People better at detecting the timing of vibrations showed stronger electroencephalogram (EEG) responses in scalp electrodes overlying the posteromedial cortex, a brain region linked to bodily awareness, Khalsa’s team reported in a preprint posted in February on bioRxiv. He hopes the buzzing pill could prove a handy way to test people’s interoceptive acuity and identify links to physical and mental health.

“One of the debates about interoceptive awareness is whether it is good to have more of it, or less,” says Wen Chen, branch chief at the National Center for Complementary and Integrative Health, who recently convened the National Institutes of Health’s first meeting on interoception research. People with conditions such as generalized anxiety disorder or irritable bowel syndrome may be “hyperfocused on sensations from their bodies,” adds Vitaly Napadow, a neuroscientist at Harvard

University's Athinoula A. Martinos Center for Biomedical Imaging. Cognitive training might help them manage overwhelming internal sensations, he says.

> **You feel a tug in your chest, and your brain has to decide if it's because you ate too much for dinner or if it's the early sign of a heart attack.**
>
> *Lisa Feldman Barrett, Northeastern University*

So might VNS, which can alter neural traffic and affect brain rhythms. Working with Cala Health, a California medical technology company, Napadow is developing a version of the ear-worn taVNS device that delivers stimulation in rhythm with a person's breathing. The design is based on brain imaging data showing the brainstem is more responsive to stimulation when a person exhales. His goal is to treat conditions such as chronic pain and migraine by boosting signals traveling through the brainstem to higher brain regions that dampen pain perception through signaling molecules such as noradrenaline and serotonin.

Scientists aren't entirely sure how vagal nerves in the human ear connect to the brain or how taVNS devices might work. But the technique offers a noninvasive alternative to surgically implanted VNS stimulators. Those devices are hard to study ethically, in part because researchers must often implant them in control group participants who will receive no electrical stimulation for long periods. The implants also require surgery to remove and can have unwanted side effects such as headaches, nausea, and cough.

Napadow's is one of more than 100 clinical trials testing taVNS—for conditions as varied as post-traumatic stress disorder, sepsis, and Alzheimer's, and even for preventing acute respiratory distress syndrome in hospitalized COVID-19 patients. The technique also holds potential as a noninvasive research tool in humans, says Nils Kroemer, a neuroscientist at the University of Tübingen, who found differences in people's motivation when stimulating the right versus the left branch of the nerve.

Other researchers are investigating whether taVNS can influence consciousness itself. At the Liège University Hospital, neurologist Steven Laureys and colleagues are planning a clinical trial of taVNS to restore awareness in people recovering from coma. Those patients occupy what researchers call the gray zone of consciousness—an intermittent, flickering awareness that is often hard to detect. Roughly one-third of people who appear completely unresponsive are at least partially conscious but can't communicate, Laureys says.

The trial builds on a recent study in which Laureys and Tallon-Baudry used interoception as a probe for consciousness in 68 coma patients. The team first identified 55 people from that group who showed signs of consciousness according to standard tests, including positron emission tomography scans, which measure brain metabolism, and MRI.

Next the researchers used EEG to record the patients' fleeting responses to their own heartbeats. A machine-learning algorithm trained to associate the heartbeat-evoked brain responses with consciousness identified with 87% accuracy which of the participants had been classified as minimally conscious using other measures, the team reported in April in *The Journal of Neuroscience*.

If the initial results hold up in larger studies, the measure could offer a simpler, cheaper way to assess consciousness in people who can't visibly react to an external stimulus such as a voice or touch. The algorithm might also predict who is most likely to respond in clinical trials such as the taVNS study. Laureys's team aims to test the safety of the device in 60 coma patients, half of whom will get electrical stimulation. The researchers will then measure their responsiveness on a standard coma recovery scale.

Neuroscientist Christof Koch of the Allen Institute for Brain Science is cautious about the heartbeat method, noting that despite being slightly more accurate than standard bedside EEG tests, it still inaccurately identified some people as conscious who weren't, which could lead to false hopes of recovery. Although machine learning can have "astounding accuracy" in distinguishing between patterns of brain activity, he adds, it doesn't reveal how those patterns drive consciousness. Still, like many other researchers, Koch is convinced that interoceptive experiences "are part and parcel of consciousness."

Fundamental questions remain about how interoceptive experiences arise—and for whom. Koch wonders, "Does a robot have the feeling that it needs to get to an electrical outlet soon when it's running out of energy?"

To Tallon-Baudry, the research in coma patients challenges a long history of thinking of bodily regulation as separate from "higher" mental processes, such as language, that constitute our sense of self. Four centuries ago, René Descartes famously conceptualized the mind as being separate from the body. But the EEG study, she says, offers a different idea of consciousness, as a subtle and private act of interoception: "just being present, as the subject of experience."

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