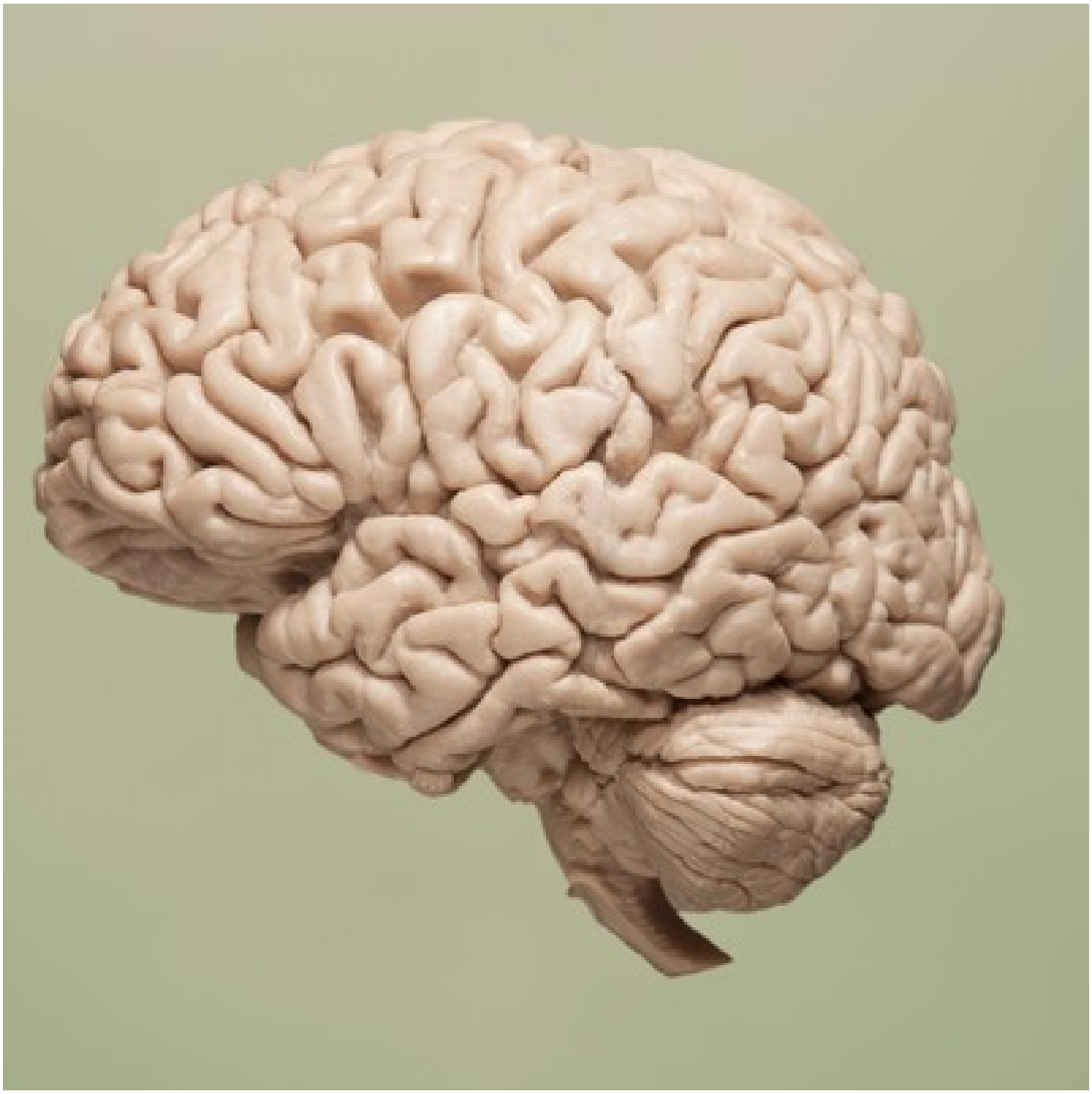

Health

This Is What Happens To Your Brain During Anesthesia

Until recently, we didn't really know.

By Shayla Love

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In the United States, almost 60,000 people receive general anesthesia during surgery every day. Through an injection, or inhalation of anesthetic gas, they safely lose consciousness while their bodies are probed and cut open. Then, their loss of consciousness is reversed. The vast majority wake up hours later, sewn up, with a gaping hole only in their memory.

"This is probably the most intense neurophysiology experiment we do in people on a regular basis," says Divya Chander, a physician, neuroscientist, and faculty member of 7 years in the department of anesthesiology at Stanford University. When she finished her PhD in neuroscience and decided to pursue anesthesiology, she says it was not only to care for patients during surgery, but to answer burning questions she's had since childhood about the very nature of being human.

"I realized, if I become an anesthesiologist, I will be afforded the great privilege of actually exploring human consciousness, manipulating human consciousness, for a living," she says.

Though we've been using anesthesia for over 170 years, for most of that time, exploring those bigger questions of consciousness wasn't possible—because we didn't really know how anesthesia worked. Anesthesia was first used in the United States in 1846 at the Massachusetts General Hospital. The drugs of choice back then were ether, chloroform and nitrous oxide, and within a

short time they were widely used across the country and around the world. Though they helped make surgery much more comfortable—their mechanism was somewhat of a mystery.

Hugh Hemmings, the anesthesiologist-in-chief at NewYork-Presbyterian Hospital/Weill Cornell Medical Center and a professor at Weill Cornell Medicine, says the root of the mystery was that so many different anesthetics could achieve the same result.

"There's really no common chemical structure that you could use to predict that a compound would be an anesthetic," he says. "That's unusual because most drugs that we know interact in a precise way with a drug receptor, or binding site, kind of like a lock and key." With anesthetics, multiple and very different chemicals could produce the same effect: loss of consciousness. How were they doing it?

One of the first theories in the late 19th century emerged when scientists found that anesthetic potency was could be predicted by how soluble it was in olive oil. They guessed that anesthetics interacted with fat, or lipid, membranes of cells in the brain. That theory persisted for decades, until in 1984, Nick Franks and Bill Lieb, at Imperial College and King's College, London, found that anesthetics could work in the absence of lipid membranes. In March of this year, Hemmings and his colleagues provided more evidence disproving the lipid theory, and confirmed that anesthetics were actually interacting with proteins in the brain.

Further study has now shown that anesthetics interact directly with a number of different proteins or cell receptors, usually to change the ways that neurons fire. Of particular research focus are ion channels and neurotransmitter receptors, like the ones that respond to GABA–one of the primary inhibitory neurotransmitters. When GABA receptors are activated they can cause the firing in a nerve cell to slow down or shut off completely.

Emery Brown is an anesthesiologist at Massachusetts General Hospital, a professor of anesthesiology at Harvard Medical School, and a Professor of Computational Neuroscience at MIT. He thinks it's great that we know the answer to the lipid-or-protein problem and that everyday we're learning more about the nitty-gritty biophysical mechanisms of anesthesia. But this knowledge alone hasn't led to a complete understanding of how it all works. "If I tell you that the drugs bind to a certain GABA receptor, you have to still answer the question, why is it that you become unconscious?" He says. "Just saying it binds to the GABA receptor cannot be the whole story."

A number of news articles and scientific reviews echo that idea: that we still don't know how anesthesia causes us to lose consciousness, despite its common, and almost mundane, use. One review from 2014 says, "Despite all the progress that has been made, we still lack a clear and comprehensive insight into the specific neurophysiological mechanisms of [general anesthesia], from the molecular level to the global brain propagation." Another from 2017 opened with, "Currently we do not understand how anesthesia leads to loss of consciousness."

But anesthesiologists, like Brown and Chander, think this attitude comes from focusing only on the molecular level, rather than on a broader neuroscientific view. Brown tells me that a growing group of anesthesiologists are taking a more holistic approach, and have been doing so for several years. They are taking advantage of how they anesthetize hundreds of people each week, and are measuring their brain activity with electroencephalograms, or EEGs, that measure the brain's electrical signals through the scalp. With that information, they're learning more about anesthesia than we've ever known before, and along with it, probing one of science's hardest and most interesting problems: the biology of consciousness.

The science of anesthesia and consciousness seem irrevocably linked, and yet, have not always been in sync. George Mashour, an anesthesiologist and neuroscientist at the University of Michigan, says that during his anesthesia fellowship, he thumbed through Miller's Anesthesia, the massive seminal anesthesia textbook, looking for a section on consciousness and couldn't find it mentioned.

"Of *all* the things that were being discussed, there was no formal discussion of it," he says. According to Mashour, in the early 2000s, a high-level neuroscientist in the field of consciousness studies was preparing for a talk to an audience of anesthesiologists. During the lecture he said that he had also searched through the index of an anesthesiology textbook to find consciousness– and could only find constipation.

Hemmings, who falls on the molecular side of anesthesia research, says that for many decades, scientists were limited by their understanding of the nervous system and of fundamental neuroscience. Now that we know more about how the brain works overall, the study of anesthesia can expand. "I'm more in the trenches at the molecular level, and others are studying the more behavioral level at the consciousness or electrophysiological levels," he says. "Merging these fields is one of our big challenges. Our meetings definitely bring together scientists in both realms. But we're not quite at the point of a full merge. But that's the ultimate goal."

Brown agrees that for this merge, researchers have to consider overall neural circuits. "Anesthesiologists have tried for years to describe anesthetic mechanism solely in terms of pharmacology," he says. "So as soon as you overlay the neuroscience, a lot of this simplifies dramatically and becomes extremely clear as to how the drugs work."

Take propofol, for example—which is one of the most common anesthetics given intravenously. If he monitors how propofol enters the brain, Brown says it travels through a major blood vessel that passes through the brainstem, where it interacts with GABA receptors and turns off arousal centers. "Now we're talking mechanism."

Brown's frequent collaborator, Patrick Purdon, a a bioengineer and neuroscientist at Massachusetts General Hospital an associate professor of anesthesia at Harvard Medical School says you might then guess that anesthetics worked by inhibiting the brain, via GABA receptors, and shutting down brain activity. "In the absence of what we know now, that's a pretty good hypothesis," he says. "But it ends up being a little more complicated. It ends up being a little more interesting."

Since Purdon and Brown have been using EEG to monitor brain activity, they could check and see if the brain simply turned off during anesthesia. Instead of seeing a quiet brain, they saw a very strong signal that looks different than any waking state. As the brain regions gradually become inhibited, a slow wave of electrical activity begins to oscillate through the brain. These oscillations change the timing of when neurons can fire, and seem to interrupt normal firing patterns and the ability of different brain regions to communicate with each other.

"Disrupting that signaling between these different areas, you can imagine, would have a disruptive effect on how the brain functions as a whole," Purdon says. "That seems to be the actual mechanism. So we make these powerful changes in the inhibitory function of the neurons, and then at a higher level what happens is that messes up the way different parts of the brain are able to function and how they're able to interact with one another."

In 2012, Purdon and Brown showed these oscillations in more detail by measuring them directly in patients with epilepsy who already had electrodes in their brains to record seizures. When they went under an anesthesia, they could record the brain waves and neuronal activity directly. "It's gating when neurons can spike," Brown says. "Therefore, it disrupts communication, so if communication is necessary for consciousness, you lose it."

Brown and Purdon think that these EEG signals are the key to understanding anesthesia. They've found that each type of anesthetic produces slightly different brain oscillations, and the oscillations can also change depending on the age of the patient. Brown has learned to notice these differences and what they mean about *how* unconscious his patients are, meaning he doesn't have to give them more anesthetic than they need. He can also tell if they're more awake than they should be.

The problem, Brown says, is most anesthesiologists don't use EEG during surgeries; they only use heart rate, blood pressure and movement as an indicator of anesthetic state. Some that do use EEG don't look at the raw waves, instead, using commercial monitors that use proprietary algorithms that provide a summary of the EEG data, which can be an oversimplification.

"The sad irony is the EEG signals under anesthesia are the strongest EEG signal that exists," Brown says. He's heard anesthesiologists say the extra measurements take too much time, or are too complicated to read. But he thinks that it's crucial to incorporate EEG into standard of care, like he's done. Since 2011, he's created a database of all of his patients' EEG signals during anesthesia, and that's how he's been able to tease apart the specific waves and what they mean.

"We've missed a tremendous opportunity to do neuroscience on a phenomenon that we uniquely control," he says. "Nobody else in neuroscience has the license to study this. I anesthetize and bring back from states of unconsciousness and anesthesia five to six people a day. A neurologist can't study that, a psychiatrist can't study that, a neurophysiologist can't study that. Think of all of the opportunity that's been wasted because we haven't taken advantage of that."

At Stanford, Chander has trained her residents to use EEG. (It was Brown who first encouraged her to use EEG in her own operating room.) Her residents learned to read the raw EEG waveforms easily, she says, but have difficulty when they go out to practice on their own. "They can't find a device or people say, 'Why would you ever want to do this?'" she says. "I just think that's a terrible shame."

Chander, like Brown, is also creating a database. So far she has about 700 patients' EEG recordings, along with "deep phenotyping"—notes of each action in surgery, whether an incision or drug given, and its effect on the brain and its activity. She's currently comparing anesthetic brain waves to those that come from sleep, coma or epileptic seizures, and is also comparing the differences in patients' brain waves when they enter and emerge from anesthesia. There's a curious feature, she says, that "you don't go down the same way you come back."

Chander thinks that not only could these oscillations lead us to better care, but back to those big questions that got her started. How the whole brain synchronizes with these slow waves, and how that disrupts the communication in the brain, lines up with some current theories of consciousness: that consciousness doesn't just exist in one specific part of the brain, but rather, is something that occurs globally, involving local activity in differing brain regions and their communication with each other.

"What am I observing as a neuroscientist?" She says she asks herself. "If our brains are basically devices that, when fully conscious, seem to calculate more information, seem to be more functionally connected, seem to be less synchronous, what does that actually mean about the underlying biological stuff that produced all that?"

She also wonders: Do brains produce consciousness simply because they are sufficiently connected and complex? Is that all we are? Can you build a machine that could be sufficiently complex? If we someday connect our brains to machines, or to other brains– will that result in higher consciousness, since it involves more connectivity?

"I have all sorts of things that are sort of percolating through in my awareness about this," she says. "I love the idea of anesthesia as this entry point I've been given to study these phenomenon

in human brains without damaging them."

Can general anesthesia really answer all those questions? Maybe not completely, Brown thinks, but it could offer new insights that weren't accessible before. "If we do our job well and give precise statements about how the anesthetics and neural circuits are inactivating the brain, then people who are looking at, what I consider to be the harder problem of consciousness, can use our information to say oh, 'That's what these circuits are doing, and here's the role that they play,'" he says.

Until then, Chander says she'll continue to marvel at the loss and gain of consciousness that she not only observes, but controls, day-to-day. She describes to me how she gives anesthetic to her patients, saying she likes to use a slow infusion of drugs. It avoids rapid changes in their heart and their respiratory systems, but also allows Chander to watch their brains go down more slowly.

"You can see as parts of the brain begin to turn off," she says. "Starting with the part of the brain that makes decisions, and responds to commands, and slowly it goes from cortex to thalamus, to their brain stem. You can watch it because their eyes begin to change and close, then their breathing begins to go away. It's just a beautiful thing."

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