SHUTTERSTOCK

THIS IS YOUR BRAIN ON ANESTHETICS

Researchers study the brain waves produced by specific drugs for a better understanding of GENERAL ANESTHESIA

JUDITH LAVELLE, C&EN WASHINGTON

WHILE YOU WERE OUT Anesthetics have been used for well over a century to put patients under, but researchers are still learning how the brain responds to these powerful drugs.

THANKS TO ANESTHETICS, patients on the operating table "sleep" through their surgery and don't feel the pain of being cut open—at least, doctors hope. But at the wrong dose, these small molecules can cause dangerous changes to heart rate, blood pressure, and a patient's ability to breathe.

To avoid catastrophe, anesthesiologists accompany the surgical team into the operating room, closely monitoring a patient's vital signs and adjusting the dose of anesthetics accordingly. Doctors have been able to regulate anesthetics in this way because they've long known how the drugs affect the heart and lungs. Surprisingly, what doctors and scientists haven't understood—and are just beginning to uncover—is how anesthetics tweak the brain to render a person unconscious.

"The drugs are acting in the brain," so it makes sense to explore the neuroscience behind how they work, says Emery N. Brown, an anesthesiologist at Massachusetts General Hospital and a professor at Massachusetts Institute of Technology.

Brown is one of an increasing number of anesthesiologists using the common neuroscience tool electroencephalography (EEG) to better understand how the brain responds to anesthetics in both research and clinical practice. Aside from explaining how the drugs cause a person's brain to lose consciousness, the data generated by this technique could play a role in improving patient safety, some scientists believe.

EEG essentially gives a readout of a person's brain waves. To take an EEG reading, researchers place electrodes on a person's scalp that measure the nerve impulses in the cerebral cortex, the outer layer of the brain that neuroscientists think is responsible for consciousness.

When researchers began monitoring raw EEG data from anesthetized patients, they noticed that each of the commonly used anesthetics—propofol, ketamine, nitrous oxide, and ether gases such as sevoflurane—consistently created distinct brain wave patterns. In recent years, Brown and his colleagues have described how these patterns correspond to the drugs' functional mechanisms in the brain to help shed light on what he calls "the mystery of anesthesia."

Brown says the patterns are easily recognizable when brain waves are plotted on a color-coded spectrogram. He even teaches undergraduates and high school students to identify them in just a 30-minute lesson. "Then we go around the operating room, and I say, 'Tell me what drug this patient is on' " just by looking at the EEG data, Brown explains.

Take propofol—a common intravenous anesthetic. The spectrogram pattern it produces has a dense region at the baseline and another dense region further up the y-axis, which corresponds to brain wave frequency. The pattern is generated by a combination of two types of brain waves: One is a "slow wave" that oscillates at less than 1 Hz, and the other is an "alpha wave" that oscillates between 8 and 12 Hz. Brown's team measured this pattern in 2013 by giving 10 healthy volunteers propofol and analyzing their EEG signatures as they dipped in and out of consciousness (*Proc. Natl. Acad. Sci. USA*, DOI: 10.1073/pnas.1221180110).

BIOCHEMICAL studies have shown that propofol binds to GABA_A receptors in a brain region called the thalamus. On the basis of their EEG data, Brown and his team deduced that propofol must slow down the nerve impulses traveling from GABA_A-decorated neurons in the thalamus up to the cerebral cortex. The "slowed down" signal transmits at a rate of 8–12 Hz, accounting for the EEG's alpha wave. The 1-Hz slow wave oscillations come from neurons across the

What doctors and scientists haven't understood is how anesthetics tweak the brain to render a person unconscious.

brain's surface switching between active and inactive states.

Brown thinks low-frequency brain waves like alpha waves and slow waves drown out the brain's normal higher-frequency activity—around 40 Hz—triggering unconsciousness. It's like how the hum of audio feedback can drown out music at a rock concert, he adds.

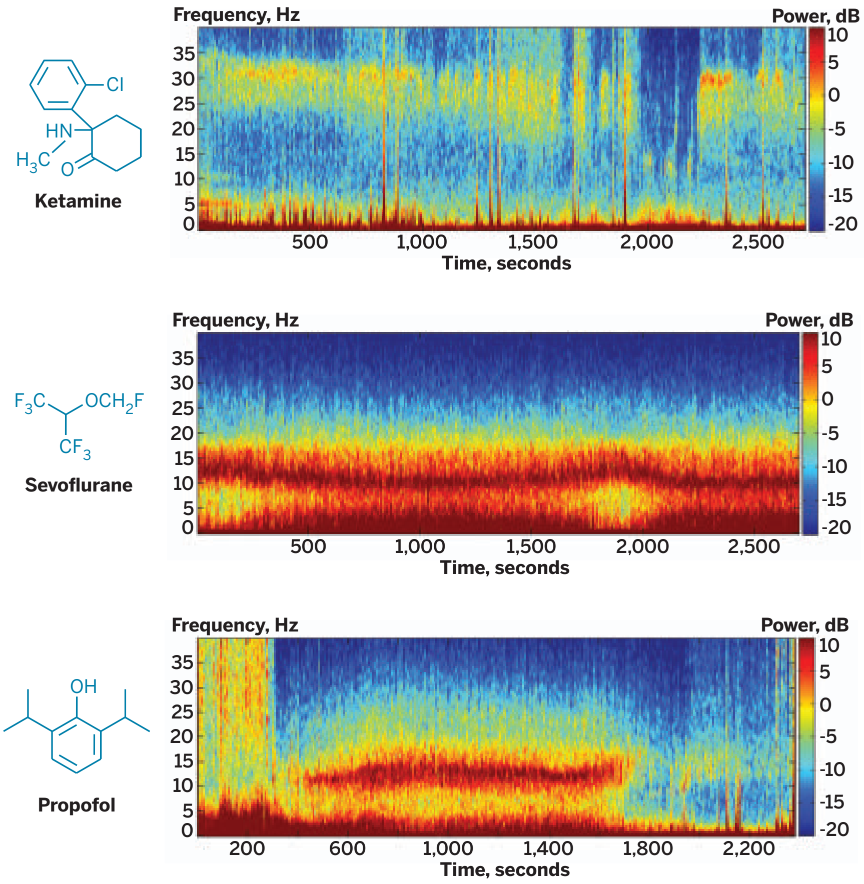
SINCE 2013, Brown's group has assessed EEG spectrograms created by other anesthetics to determine their unique signatures, which can be linked to their known biochemical pathways for a more holistic picture of their action in the brain. Most recently, the researchers have published on the brain waves produced by nitrous oxide, one of the oldest anesthetics still in use (*Clin. Neurophysiol.* 2015, DOI: 10.1016/j.clinph.2015.06.001).

Roderic G. Eckenhoff, an anesthesiologist at the University of Pennsylvania who investigates the molecular binding activity of anesthetic drugs, says approaches like Brown's may play an important role in answering the question of how anesthetics induce unconsciousness. "EEG is not going to answer it. Playing with molecules and proteins like I do is not going to answer it," Eckenhoff says. "You need the host of approaches to tackle this issue."

Brown also uses EEG in his clinical practice and says monitoring the brain waves of patients during surgery gives him the confidence to administer more tailored, refined doses of anesthetics. It would've been nice in the past, he says, to be able to dial back the anesthetic dose being given to a patient if that person were sufficiently unconscious. But without knowing exactly what the brain was doing, he didn't want to risk a patient waking up during surgery.

> **"With this information, you are now an open book."**

DISTINCTIVE Each anesthetic produces a unique brain wave pattern, as revealed by EEG data. The power in decibels of a brain wave's frequency—measured in hertz along the y-axis—is color-coded from red (high) to blue (low).



PARTNER'S HEALTHCARE/AMERICAN SOCIETY OF ANESTHESIOLOGISTS

Brain monitoring technologies such as EEG are often present but not routinely used in today's operating rooms. Most anesthesiologists base the amount of anesthetic they give on a patient's vital signs, whether or not they begin to move, and their medical history. But as research like Brown's reveals more about how anesthetics affect the brain, some believe brain monitoring could lead to better patient safety.

MOST ANESTHESIOLOGISTS who monitor brain activity in the clinic don't look at raw EEG data. Instead they use a device called a bispectral index (BIS) monitor, which reduces EEG information to a single number that indicates the extent of a person's wakefulness. Barry Friedberg, an anesthesiologist who advocates for incorporating brain monitoring as a standard of care, uses a BIS monitor on his patients as well as electromyography (EMG), which measures muscle activity around the scalp that's indicative of wakefulness. "What I tell patients is, 'look, before I had this ability to see how your brain responded, you came to me as a mystery I had to solve,'" says Friedberg. "'With this information, you are now an open book.'"

Some anesthesiologists argue more precise doses could avoid potentially severe consequences from overmedication. Although clinical studies have yet to confirm and quantify the phenomenon, doctors have observed that some elderly patients may experience lasting cognitive impairment after surgery, and it's unclear whether too high a dose of anesthetics could be responsible. Brown believes his EEG studies may shed light on how this could occur in the brain.

Whether being used in medical practice or in fundamental research, brain waves seem as though they could help reveal the important mechanisms behind drugs that have been used for over a century. "The more educated, principled, physiology-based approach," Brown says, "is what we're trying to foster by helping anesthesiologists not only use EEG but also understand the neuroscience behind why the patterns come about as they do for specific drugs." ■