You Must Remember This

What stays with us, and what we forget, depends in part on how well our neurons keep time

BY CHRISTOF KOCH

Unusual and emotionally resonant events are particularly indelible. But the natural rhythms of the brain also play a role in what we recall.

CHRISTOF KOCH (*Koch*); GETTY IMAGES (*old photographs*)

ONE OF THE SIGNATURE discoveries of cognitive neuroscience is that a structure called the hippocampus, deep within the brain, is intimately involved in creating memories. This fact was dramatically illustrated by a singular patient, Henry Molaison, who experienced severe epileptic seizures. In 1953, when Molaison was 27, doctors removed his hippocampus and nearby areas on both sides of his brain. The operation controlled his epilepsy, but at a price—from that time on, he was unable to remember the things that happened to him. He could learn skills, such as mirror writing, but would be puzzled by his expertise, because he could not recall having acquired it.

H.M., as he was known during his lifetime to protect his privacy, taught scientists three lessons. First, certain brain structures—the hippocampus and the amygdala, the brain's emotion center—specialize in remembering. Second, there are different kinds of memory—the ability to recall facts, or personal experiences, or physical skills like riding a bike—each with its own properties. Third, memory is distinct from the brain's intellectual and perceptual abilities.

Fifty years later these conclusions have been strengthened by laboratory studies on mice, rats and monkeys and by further clinical observation. A case in point is transient global amnesia, a rare but enigmatic loss of memory that is sometimes triggered by a stressful event. The patient suddenly cannot recall facts or experiences—anything that is not deeply encoded, such as his name. He also becomes unable to form new memories. There is no impairment in motor or sensory function, judgment, intellectual faculties or consciousness. As the name suggests, transient global amnesia is temporary, disappearing within 24 hours with little long-term effect. But within a day or two of the attack, high-resolution imaging reveals small areas of damage in a specific part of the hippocampus.

Having established the critical role of the hippocampus, the next question is: What makes something memorable? Of the countless things a person encounters in a given day, why do some become indelibly imprinted, whereas others vanish like soap bubbles? Scientists know that many factors play a role in determining what people remember, among them how much attention the person is paying, how novel and interesting the experience is, and the kinds of emotions that are evoked. But recently a team led by neuroscientist Ueli Rutishauser of the Howard Hughes Medical Institute at the California Institute of Technology delved into the cellular workings of the hippocampus, chronicling the activity of individual brain cells as people absorbed and recalled new information. Their findings, though delivered in the technical language of action potentials and electrical frequencies, provide intriguing insights into the Proustian mystery of memory.

Electrodes Thinner Than a Hair

Epilepsy treatments, though less invasive than in H.M.'s day, continue to offer unique opportunities for neuroscientific insight. To pinpoint where seizures originate, doctors sometimes implant electrodes thinner than a hair in the affected brain areas. Then for a few days they eavesdrop on the electrical activity that takes place while the patient talks, watches television, moves around and sleeps in the hospital ward.

Rutishauser and his colleagues piggybacked their memory experiment on this medical protocol. They asked nine epileptics who were undergoing electrode monitoring to view 100 slides, each of which showed an image of a person, an animal, or an everyday object such as a car or a tool. The patients had one second to commit each picture to memory as best they could before the next one appeared. The team later tested the patients' recall by showing them a second set of 100 photographs, half of which were novel and half of which were repeats from the ini-

> How do **three pounds of viscous tissue** hold a lifetime of accumulated impressions, recollections and knowledge?

tial slide show, and asking them to identify which ones they had already seen. During the two slide shows, the team used the implanted microelectrodes to track electrical activity in the hippocampus and the amygdala.

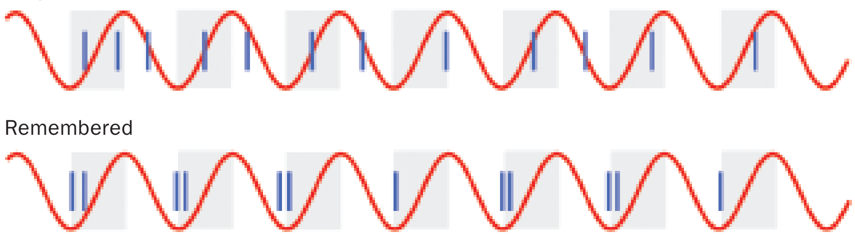
The electrical fields that are picked up by this technique include a variety of rhythms. Delta waves—slow brain waves that occur one to four times a second—are characteristic of deep sleep. Beta waves, which occur 12 to 30 times per second, dominate when people are actively concentrating.

At a middle tempo is the theta rhythm, which repeats three to 10 times per second. (To put this in perspective, consider that when I run along the steep trails in the San Gabriel Mountains, my heart rate plateaus at 160 beats per minute, or 2.6 beats per second.)

The theta rhythm is particularly strong when people are finding their way or looking at something novel—in other words, when they are learning. Previous experiments suggest that the stronger these oscillations are and the more often they occur during learning, the better the person will remember the new material.

So it was not a surprise that the Rutishauser team picked up prominent theta activity when the patients were memorizing the images. But their findings went deeper. Using sensitive electronics and sophisticated software, the scientists could detect the faint staccato sounds that individual neurons make as they send information to one another by way of all-or-none pulses known as spikes.

The team recorded the activity of 305 neurons in the hippocampus and the amygdala. The total number of spikes that occurred while a subject viewed an image did not predict whether or not the patient would later recall it. (On average, participants recognized two out of three of the initial pictures.) Yet the scientists found something that did predict successful recall in about one fifth of cells.



Scientists recorded the activity of individual neurons (*blue lines*) during a memory task. TOP: Neurons fire randomly, and the information is not retained. BOTTOM: Neurons spike during regular troughs in the theta wave (*red line*), which dominates during learning; recall improves.

Getting into a Groove

Nerve cells do not generally operate in lockstep. They typically send out pulses irregularly, whenever their excitation levels exceed a threshold. What the Caltech team found, however, is that neuronal rhythms can be highly orchestrated at times—and that this synchrony helps people form lasting memories. Think about a freestyle swimmer. She regularly turns her head to the side to breathe within the triangle formed by her upper and lower arm and the waterline. If she takes a breath during a different phase of the crawl, she most likely will swallow water and lose her rhythm. And so it seems to be for these memory-forming neurons.

During the learning phase, the team found, if a picture flashed on the screen at a moment when neuronal spikes in the hippocampus and the amygdala lined up with the local theta clock, patients were more likely to remember the image and feel confident that their recollection was accurate [*see illustration at left*]. When people were viewing images that they would later fail to recognize, this coordination between individual memory-encoding neurons and overall brain activity was much reduced.

This research reveals an extra factor besides attention, novelty and emotional impact in determining what makes something memorable: timing. Neurons always spike in response to new images and experiences. But when the spikes happen to coincide with the theta rhythm, this coordinated electrical activity alters the brain's synapses, those specialized molecular machines between neurons, enabling memories to form.

These subtle findings help to decode the mechanics of memory—how three pounds of viscous tissue produces a mind possessed of innumerable impressions, recollections and knowledge accumulated over the course of decades. **M**

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(Further Reading)

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- **Human Memory Strength Is Predicted by Theta-Frequency Phase-Locking of Single Neurons.** Ueli Rutishauser, Ian B. Ross, Adam N. Mamelak and Erin M. Schuman in *Nature,* Vol. 464, pages 903–907; April 8, 2010.
- **Focal Lesions of Human Hippocampal CA1 Neurons in Transient Global Amnesia Impair Place Memory.** T. Bartsch et al. in *Science,* Vol. 328, pages 1412–1415; June 11, 2010.

SOURCE: UELI RUTISHAUSER