

Searching for the Memory

New research sheds light—literally—on recall mechanisms

BY CHRISTOF KOCH



The difference between false memories and true ones is the same as for jewels: it is always the false ones that look the most real, the most brilliant.

gion as far as learning is concerned.

The most singular feature of science that distinguishes it from other human activities, such as art or religion, and gives it a dynamics of its own, is prog-

page 76], and you will not be able to form new explicit memories, whereas losses of large swaths of visual cortex leave the subjects blind but without memory impairments.

Yet percepts and memories are not born of brain regions but arise within intricate networks of neurons, connected by synapses. Neurons, rather than chunks of brain, are the atoms of thoughts, consciousness and remembering.

Implanting a False Memory in Mice

If you have ever been the victim of a mugging in a desolate parking garage, you may carry that occurrence with you to the end of your days. Worse, whenever you walk into a parking structure, you become anxious, your heart rate goes up and you begin to sweat. You have been fear-conditioned by the event. Fear conditioning has proved to be a fruitful avenue into the molecular and neuronal basis of learning and remembering.

Mice, the experimental animals of choice, can easily be fear-conditioned by placing them in one particular environmental context—say, a chamber with black walls, white floor, dim lighting and the smell of vinegar—and applying brief electrical shocks to the floor under their paws. If the mouse is returned to this cage the next day, it “freezes” in place, becoming totally immobile for a fraction of a minute or longer, in anticipation of another shock. Freezing is an instinctual reaction to threats, as most predators are wired to look for movements to pinpoint their next meal. Put the mouse into an

THIS QUOTE by surrealist painter Salvador Dalí comes to mind when pondering the latest wizardry coming out of two neurobiology laboratories. Before we come to that, however, let us remember that ever since Plato and Aristotle first likened memories to impressions made onto wax tablets, philosophers and natural scientists have searched for the physical substrate of memories. In the first half of the 20th-century psychologists carried out carefully controlled experiments to look for the so-called memory engram in the brain.

One of the most influential was Karl Lashley of Harvard University. He trained rats to run through mazes, turning left here and right over there, to find bits of food. Lashley would then make lesions in various parts of their cerebral cortex, the highly convolved sheet of neurons crowning the brain and situated just underneath the skull. He crystallized the insights he obtained in his lifelong efforts in two maxims. His principle of mass action stipulated that the cerebral cortex is holistically involved in memory storage. That is, the more cortex that is destroyed, the worse the memory of the animal, with no regard to what specific part of the cortex is removed. Indeed, according to Lashley’s second principle, of equipotentiality, any area of cortex can substitute for any other re-



ress. It results from the steady and cumulative accumulation of knowledge, the emendation and cleansing of inaccuracy and inconsistency, and the understanding that comes from constantly querying nature through empirical investigation coupled with theory. In the case of the physical substrate of memories, today’s neuroscience research has turned Lashley’s two principles on their head. We now know that certain brain structures, such as the hippocampus, are involved in specific types of memory. Lose that region on both sides of the brain, such as the unfortunate patient HM did [see “Mind in Pictures,” on

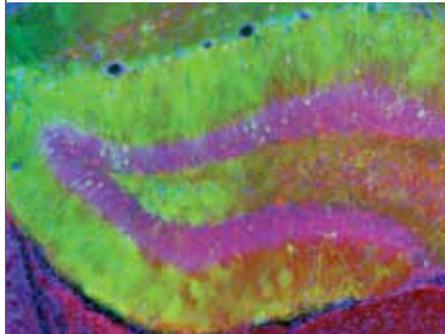
CHRISTOF KOCH (Koch); RALF HIEMISCH/Getty Images (man with maze)

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environment that looks and smells different from the one it was conditioned in, and much less freezing occurs.

Two American teams of researchers, one at the Massachusetts Institute of Technology led by Susumu Tonegawa and a second one under Mark Mayford of the Scripps Research Institute in La Jolla, Calif., exploited this standard test to manipulate the engram for this scary event. Part of the engram is found in the dentate gyrus (DG), a substructure of the hippocampus in the M.I.T. study, whereas the Scripps study did not specify the location of the engram. Shocking an animal in one context will activate a small subset of DG neurons, around 2 to 4 percent. A different context will be encoded by a separate sparse group of DG cells. The electrical activity in these cells triggers the expression of a small number of so-called immediate early genes. Both groups used mice that were genetically manipulated so that the increased production of one of these genes within a particular time window triggers a cascade of cellular events that ultimately leaves a permanent molecular tag on the cell that can be made to glow. This labeling allowed the experimentalists to later identify and reactivate the same set of previously firing neurons using either beams of blue light introduced via fiberoptic cable (the M.I.T. group) or by delivery of a drug not naturally present in the animal (the Scripps group). These manipulations—deep-brain stimulation on steroids—are made possible by the fantastic marriage of three technologies: pharmacology, optical stimulation and molecular biology [see “Playing the Body Electric,” by Christof Koch; *SCIENTIFIC AMERICAN MIND*, March/April 2010].

Now I will concentrate on the findings from M.I.T. They had a group of mice explore one particular environment (let’s call it A). Later on, bombarding the DG with blue light triggered the minority of neurons that had been active



Tagging neurons in the dentate gyrus, part of the hippocampus deep inside the brain, with specific proteins allows the astute experimentalist to track down and manipulate memories. Perhaps one day these technologies can be adopted to delete old memories and implant new ones at will?

while the rodents were getting used to this context. A few days later the same animals were placed into a new context—cages thlooked and smelled different (environment B)—while they were electrically shocked. This robustly activated DG neurons that were furiously encoding anything and everything about this obviously dangerous place so that the mice could avoid it in future. As in all these transgenic mice, the activity molecularly labels these cells for subsequent reactivation.

In the crux of the experiment, the rodents were dropped into the neutral environment A that they had no cause to fear. Indeed, without blue light these animals did not show any freezing. Yet in a beautiful confirmation of the power of optogenetics, when the blue light was turned on, the mice froze! Triggering the neurons that encoded environment B, including its association with the painful shock, induced the memory and made the mice cower in expectation of some-

thing bad about to happen. That is, neural circuits in the dentate gyrus of the hippocampus wired up to express an aversive event that happened at B are sufficient to evoke the associated aversive memory, even though the subjects never had experienced anything bad in A. It is an artificial memory—think *Total Recall*—but to the mice it appeared real enough that they went into their defensive crouch.

This experiment proves that activating on the order of 10,000 interlaced neurons in one very specific region of the brain is *sufficient* for a specific memory, its engram. Whether these circuits are also *necessary* for this memory, that is, whether deleting these neurons will remove the memory—shades of *Eternal Sunshine of the Spotless Mind*—remains to be determined (soon).

Let me end with another evocative quote from a film that routinely tops the list of the best science-fiction movies ever. I leave it to you, esteemed reader, to discover its source. It is a death soliloquy that speaks to the clarity and lucidity of memories, real or false ones:

I’ve seen things you people wouldn’t believe. Attack ships on fire off the shoulder of Orion. I’ve watched c-beams glitter in the dark near the Tannhäuser Gate. All those moments will be lost in time, like tears in rain. Time to die. M

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(Further Reading)

- ◆ **Optogenetic Stimulation of a Hippocampal Engram Activates Fear Memory Recall.** X. Liu et al. in *Nature*. Published online March 22, 2012.
- ◆ **Generation of a Synthetic Memory Trace.** A. R. Garner et al. in *Science*, Vol. 335, pages 1513–1516; March 23, 2012.

FROM SUPPLEMENTARY MATERIAL IN “OPTOGENETIC STIMULATION OF A HIPPOCAMPAL ENGRAM ACTIVATES FEAR MEMORY RECALL,” BY X. LIU ET AL., IN *NATURE*. PUBLISHED ONLINE MARCH 22, 2012