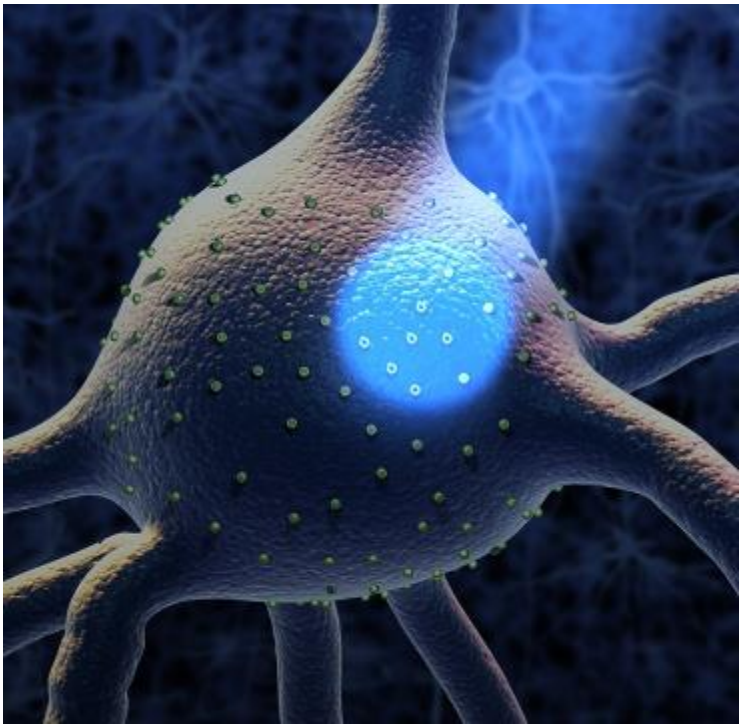
Scientists recover 'lost' memories using brain stimulation by blue light

Amnesia is a fixable result of retrieval impairment, not damage

May 29, 2015



MIT researchers have found they were able to reactivate memories in mice that could not otherwise be retrieved, using optogenetics — in which proteins are added to neurons to allow them to be activated with light.

The breakthrough finding, in a paper published Thursday (May 28) in the journal *Science*, appears to answer a longstanding question in neuroscience regarding amnesia.

Damaged or blocked memory?

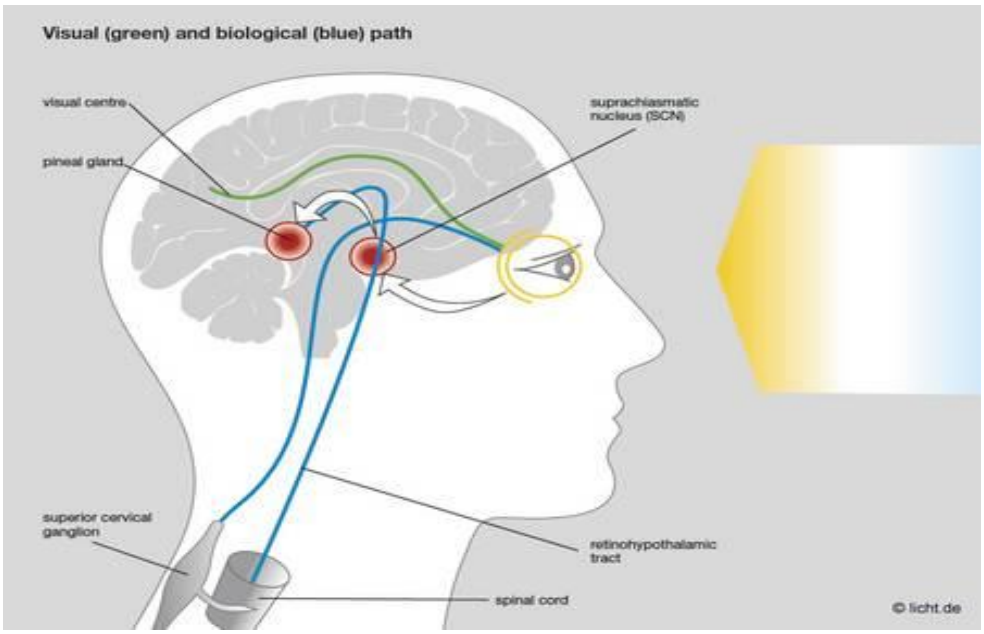
Neuroscience researchers have for many years debated whether retrograde amnesia — which follows traumatic injury, stress, or diseases such as Alzheimer's — is caused by damage to specific brain cells, meaning a memory cannot be stored, or if access to that memory is somehow blocked, preventing its recall.

The answer, according to Susumu Tonegawa, the Picower Professor in MIT's Department of Biology and director of the RIKEN-MIT Center at the Picower Institute for Learning and Memory: "Amnesia is a problem of retrieval impairment."

Memory researchers have previously speculated that somewhere in the brain network is a population of neurons that are activated during the process of acquiring a memory, causing enduring physical or chemical changes.

If these groups of neurons are subsequently reactivated by a trigger such as a particular sight or smell, for example, the entire memory is recalled. These neurons are known as "memory engram cells."

Recent studies confirm that light has another important function: it synchronises our internal clock – the complex system that coordinates all our bodily functions in a 24-hour rhythm.



Third photoreceptor in the eye

The biological effectiveness of light is possible thanks to a third photoreceptor in the eye discovered by scientists in 2002. Prior to that, only two types of receptor were known: cones for colour vision and more light-sensitive rods, which enable us to see even when illuminanceis low. But a few years ago, researchers discovered special ganglion cells in the retina that do not have a visual function. They contain a light-sensitive pigment called melanopsin and respond very sensitively to the blue content of light.

From IMUNE medical textbooks : :
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Blocking, then activating memories with light

Until now, no one has been able to show that these groups of neurons undergo enduring chemical changes, in a process known as memory consolidation. One such change, known as “long-term potentiation” (LTP), involves the strengthening of synapses, the structures that allow groups of neurons to send signals to each other, as a result of learning and experience.

To find out if these chemical changes do indeed take place, the researchers first identified a group of engram cells in the hippocampus that, when activated using optogenetic tools, were able to express a memory.

When they then recorded the activity of this particular group of cells, they found that the synapses connecting them had been strengthened. “We were able to demonstrate for the first time that these specific cells — a small group of cells in the hippocampus — had undergone this augmentation of synaptic strength,” Tonegawa says.

The researchers then attempted to discover what happens to memories without this consolidation process. By administering a compound called anisomycin, which blocks protein synthesis within neurons, immediately after mice had formed a new memory, the researchers were able to prevent the synapses from strengthening.

When they returned one day later and attempted to reactivate the memory using an emotional trigger, they could find no trace of it. “So even though the engram cells are there, without protein synthesis those cell synapses are not strengthened, and the memory is lost,” Tonegawa says.

But startlingly, when the researchers then reactivated the protein synthesis-blocked engram cells using optogenetic tools, they found that the mice exhibited all the signs of recalling the memory in full.

“If you test memory recall with natural recall triggers in an anisomycin-treated animal, it will be amnesiac, you cannot induce memory recall,” Tonegawa says. “But if you go directly to the putative engram-bearing cells and activate them with light, you can restore the memory, despite the fact that there has been no LTP.”

Memories are stored in a circuit of groups of cells in multiple brain areas, not synapses

Further studies carried out by Tonegawa's group demonstrated that memories are stored not in synapses strengthened by protein synthesis in individual engram cells, but in a circuit, or "pathway" of multiple groups of engram cells and the connections between them.

"We are proposing a new concept, in which there is an engram cell ensemble pathway, or circuit, for each memory," he says. "This circuit encompasses multiple brain areas and the engram cell ensembles in these areas are connected specifically for a particular memory."

The research dissociates the mechanisms used in memory storage from those of memory retrieval, according to Ryan. "The strengthening of engram synapses is crucial for the brain's ability to access or retrieve those specific memories, while the connectivity pathways between engram cells allows the encoding and storage of the memory information itself," he says.

Changes in synaptic strength and in spine properties have long been associated with learning and memory, according to Alcino Silva, director of the Integrative Center for Learning and Memory at the University of California at Los Angeles.

"This groundbreaking paper suggests that these changes may not be as critical for memory as once thought, since under certain conditions, it seems to be possible to disrupt these changes and still preserve memory," he says. "Instead, it appears that these changes may be needed for memory retrieval, a mysterious process that has so far evaded neuroscientists."

Abstract of *Engram cells retain memory under retrograde amnesia*

Memory consolidation is the process by which a newly formed and unstable memory transforms into a stable long-term memory. It is unknown whether the process of memory consolidation occurs exclusively through the stabilization of memory engrams. By using learning-dependent cell labeling, we identified an increase of synaptic strength and dendritic spine density specifically in consolidated memory engram cells. Although these properties are lacking in engram cells under protein synthesis inhibitor–induced amnesia, direct optogenetic activation of these cells results in memory retrieval, and this correlates with retained engram cell–specific connectivity. We propose that a specific pattern of connectivity of engram cells may be crucial for memory information storage and that strengthened synapses in these cells critically contribute to the memory retrieval process.

references:

- Tomas J. Ryan et al. Engram cells retain memory under retrograde amnesia. Science 29 May 2015: Vol. 348 no. 6238 pp. 1007-1013 DOI: 10.1126/science.aaa5542
- Tomás J. Ryan, Dheeraj S. Roy, Michele Pignatelli, Autumn Arons, and Susumu Tonegawa. Engram cells retain memory under retrograde amnesia. Science, 29 May 2015: 1007-1013 DOI: 10.1126/science.aaa5542

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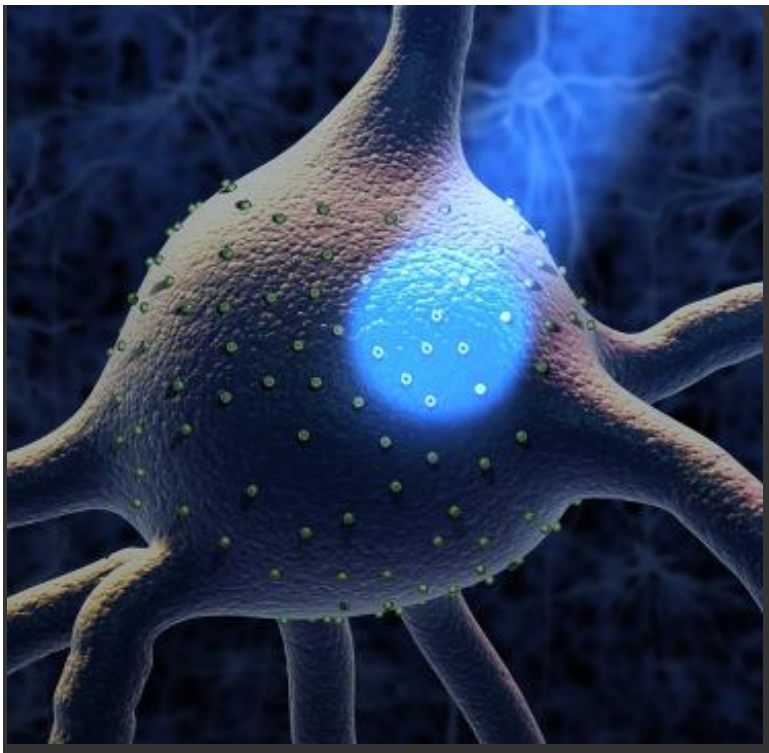
Wake Forest Baptist Medical Center researchers are gaining a better understanding of the neurochemical basis of addiction with a new technology called optogenetics.

In neuroscience research, optogenetics is a newly developed technology that allows researchers to control the activity of specific populations of brain cells, or neurons, using light. And it's all thanks to understanding how tiny green algae, that give pond scum its distinctive color, detect and use light to grow.

The technology enables researchers like Evgeny A. Budygin, Ph.D., assistant professor of neurobiology and anatomy at Wake Forest Baptist, to address critical questions regarding the role of dopamine in alcohol drinking-related behaviors, using a rodent model.

"With this technique, we've basically taken control of specific populations of dopamine cells, using light to make them respond – almost like flipping a light switch," said Budygin. "These data provide us with concrete direction about what kind of patterns of dopamine cell activation might be most effective to target alcohol drinking."



Researchers used cutting-edge molecular techniques to express the light-responsive channelrhodopsin protein in a specific population of dopamine cells in the brain-reward system of rodents. They then implanted tiny optical fibers into this brain region and were able to control the activity of these dopamine cells by flashing a blue laser on them. This illustrative image is credited to McGovern Institute for Brain Research and Sputnik Animation.

The latest study from Budygin and his team published online in last month's journal *Frontiers in Behavioral Neuroscience*. Co-author Jeffrey L. Weiner, Ph.D., professor of physiology and pharmacology at Wake Forest Baptist, said one of the biggest challenges in neuroscience has been to control the activity of brain cells in the same way that the brain actually controls them. With optogenetics, neuroscientists can turn specific neurons on or off at will, proving that those neurons actually govern specific behaviors.

"We have known for many years what areas of the brain are involved in the development of addiction and which neurotransmitters are essential for this process," Weiner said. "We need to know the causal relationship between neurochemical

changes in the brain and addictive behaviors, and optogenetics is making that possible now."

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"You can place an electrode in the brain and apply an electrical current to mimic the way brain cells get excited, but when you do that you're activating all the cells in that area," Weiner said. "With optogenetics, we were able to selectively control a specific population of dopamine cells in a part of the brain-reward system. Using this technique, we discovered distinct patterns of dopamine cell activation that seemed to be able to disrupt the alcohol-drinking behavior of the rats."

Weiner said there is translational value from the study because "it gives us better insight into how we might want to use something like deep-brain stimulation to treat alcoholism. Doctors are starting to use deep-brain stimulation to treat everything from anxiety to depression, and while it works, there is little scientific understanding behind it, he said.

Budygin agreed and said this kind of project wouldn't be possible without cross campus collaboration between neurobiology and anatomy, physiology and pharmacology and physics. "Now we are taking the first steps in this direction," he said. "It was impossible before the optogenetic era."

Notes about this optogenetics and addiction research

The study was supported by the National Institutes of Health T32 AA007565, AA020564, AA021099, AA017531, AA010422, and DA024763.

Co-authors include Valentina P. Grinevich, Dominic Gioia, Jon Day-Brown, Keith D. Bonin, all of Wake Forest Baptist; Garret D. Stuber of UNC Neuroscience Center and Caroline E. Bass of University of Buffalo.

phys.org/news/2015-03-particle.html

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The first ever photograph of light as both a particle and wave

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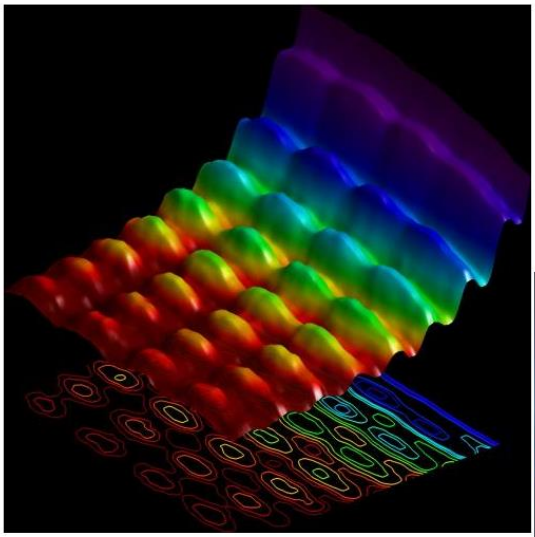
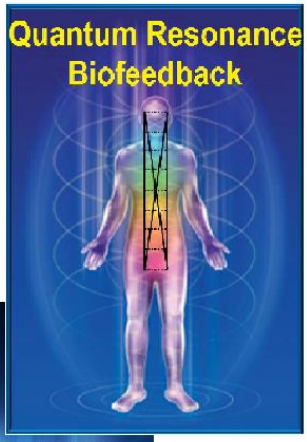
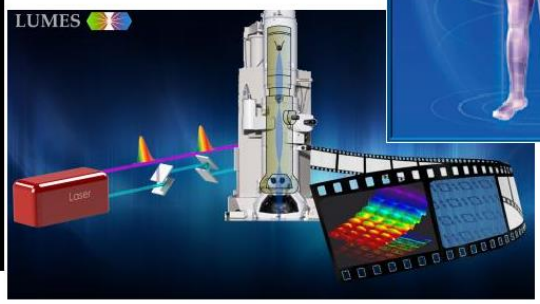


Quantum mechanics tells us that light can behave simultaneously as a particle or a wave. However, there has never been an experiment able to capture both natures of light at the same time; the closest we have come is seeing either wave or particle, but always at different times. Taking a radically different experimental approach, EPFL scientists have now been able to take the first ever snapshot of light behaving both as a wave and as a particle. The breakthrough work is published in *Nature Communications*.





(Phys.org)—Light behaves both as a particle and as a wave. Since the days of Einstein, scientists have been trying to directly observe both of these aspects of light at the same time. Now, scientists at EPFL have succeeded in capturing the first-ever snapshot of this dual behavior.

When UV light hits a metal surface, it causes an emission of electrons. Albert Einstein explained this "photoelectric" effect by proposing that light – thought to only be a wave – is also a stream of particles. Even though a variety of experiments have successfully observed both the particle- and wave-like behaviors of light, they have never been able to observe both at the same time.

A research team led by Fabrizio Carbone at EPFL has now carried out an experiment with a clever twist: using electrons to image light. The researchers have captured, for the first time ever, a single snapshot of light behaving simultaneously as both a wave and a stream of particles.

The experiment is set up like this: A pulse of laser light is fired at a tiny metallic nanowire. The laser adds energy to the charged particles in the nanowire, causing them to vibrate. Light travels along this tiny wire in two possible directions, like cars on a highway. When waves traveling in opposite directions meet each other they form a new wave that looks like it is standing in place. Here, this standing wave becomes the source of light for the experiment, radiating around the nanowire.

This is where the experiment's trick comes in: The scientists shot a stream of electrons close to the nanowire, using them to image the standing wave of light. As the electrons interacted with the confined light on the nanowire, they either sped up or slowed down. Using the ultrafast microscope to image the position where this change in speed occurred, Carbone's team could now visualize the standing wave, which acts as a fingerprint of the wave-nature of light.

While this phenomenon shows the wave-like nature of light, it simultaneously demonstrated its particle aspect as well. As the electrons pass close to the standing wave of light, they "hit" the light's particles, the photons. As mentioned above, this affects their speed, making them move faster or slower. This change in speed appears as an exchange of energy "packets" (quanta) between electrons and photons. The very occurrence of these energy packets shows that the light on the nanowire behaves as a particle.

"This experiment demonstrates that, for the first time ever, we can film quantum mechanics – and its paradoxical nature – directly," says Fabrizio Carbone. In addition, the importance of this pioneering work can extend beyond fundamental science and to future technologies. As Carbone explains: "Being able to image and control quantum phenomena at the nanometer scale like this opens up a new route towards quantum computing."