Mysterious brain activity in mice watching a movie could help tackle Alzheimer's, improve AI

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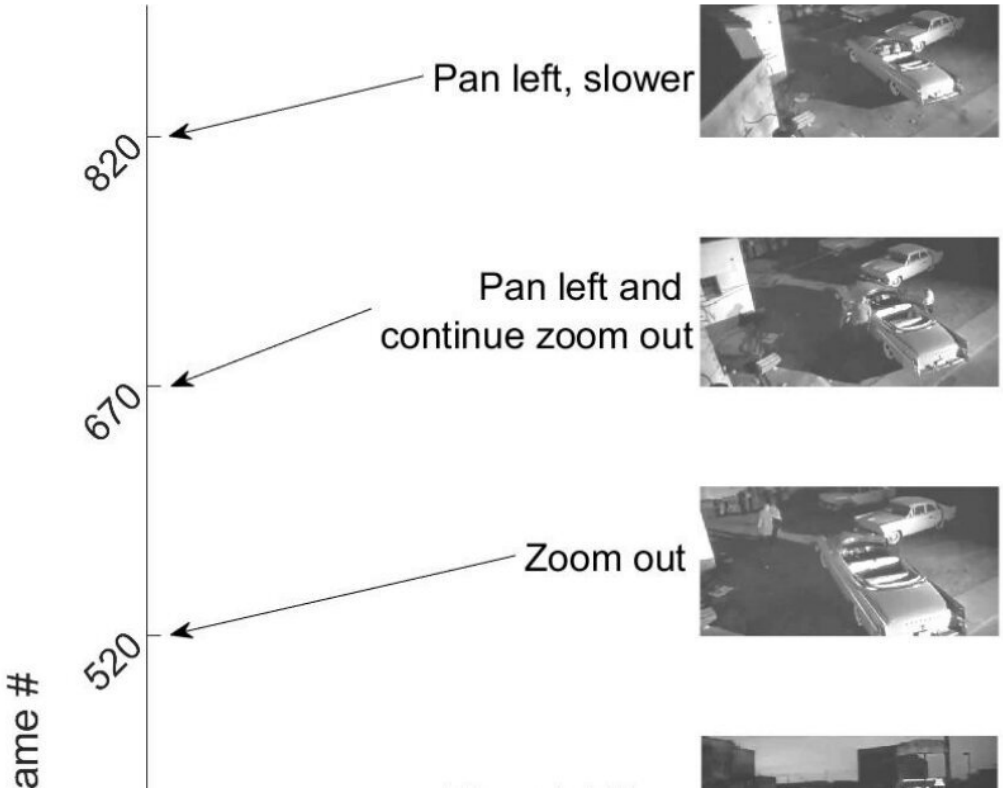

The movie. The 30 second long, isoluminant movie with frame numbers denoting key episodes in this continuous segment. Credit: *elife* (2023). DOI: 10.7554/eLife.85069.1

Even the legendary filmmaker Orson Welles couldn't have imagined such a plot twist.

By showing Welles's movie "Touch of Evil" to mice, Chinmay Purandare, Ph.D., and Prof. Mayank Mehta of UCLA have uncovered surprising and important new insights about how neurons form memories. The discovery points to new ways to diagnose Alzheimer's and other learning and memory impairments, while also improving artificial intelligence.

Mice were shown a short clip from the 1958 film noir classic "Touch of Evil" as scientists monitored their brain activity. This was a rather nondescript black-and-white, silent movie clip showing humans walking about. Textbook knowledge and conventional wisdom says that mice should not show interest in such a movie and nor should neurons in a part of their brain called the hippocampus, which is known to be crucial for learning and memory.

When scientists looked inside this part of the mouse brain, they found that it only acts as "the GPS system of the brain" (as described in the 2014 Nobel Prize in Physiology or Medicine), which is unrelated to general learning, e.g. a conversation. This was a major obstacle in research on diagnosis of memory and on mechanisms of abstractions or AI.

However, the researchers made a blockbuster finding: There were surprising, but highly systematic bursts of activity in the hippocampus in response to this movie. Scientists could even reconstruct specific movie segments using these mysterious bursts from only a fraction of hippocampal neurons.

The plot thickens even more. Even neurons in other parts of the brain (the primary visual cortex or the thalamus) that are commonly thought to

encode simple features like vertical or horizontal lines responded far more robustly to the specific scenes of the movie than the textbook stimuli. In fact, every part of the brain that they investigated, from the simple visual to the GPS circuits, lit up robustly in response to specific movie scenes.

Mehta said the findings represent a "major paradigm shift" in how scientists can study mice's ability to recall a specific experience or event—or what's known as episodic memory. Mehta said this could help scientists address a missing component in research for memory diseases like Alzheimer's.

"Although dozens of drugs have cured Alzheimer's in mice, none have worked in humans," Mehta said. "One reason is that the standard test of episodic learning and memory is spatial navigation in mice. However, Alzheimer's patients have profound deficits in non-spatial memory too—e.g., a conversation or an event they witnessed, which is unrelated to GPS navigation."

The authors say that focusing Alzheimer's and other memory drugs in mice using only a spatial memory test doesn't address whether the treatments improved the mice's ability to remember most events or experiences that make up episodic memory.

"It is a major challenge to create such events for mice that would closely mimic events familiar to humans. Hence, we turned to movies," said Dr. Purandare, the study's lead author. "By all textbook accounts, human movies should not generate any interpretable pattern in the mouse hippocampus."

However, in the studies published in *Nature* in 2021 and 2022, these UCLA researchers found that neurons in the mice hippocampus responded to simple visual stimuli when mice explored virtual reality and

this induced robust neuroplasticity. Therefore, they theorized it was possible to test episodic memory in mice by showing them a movie and monitoring activity in their hippocampus.

In this new study, nearly half of neurons in the rodent hippocampus encoded specific, small segments of the movie, signifying a remarkable response to the events on screen. The mundanity of the silent, black-and-white clip made the findings even more compelling, Mehta said. In fact, mice were also free to ignore the movie if they wanted to.

"If the hippocampus lights up with this mundane movie clip, without any memory demand, then we can safely conclude that it is not due to other things like expectation of reward or excitement," Mehta said. "We were blown away by the massive responses despite the lack of these emotional components."

Mehta said preliminary data indicated that making the scene richer by adding interesting elements for mice, like images of other animals, sounds, etc. could produce a stronger hippocampal response, creating an emotional response and vibrant episodic memories.

"Another major surprise, the visual areas did not care if the movie was played in a sequence, or in a scrambled order. But the hippocampal neurons did something very different—they did not respond at all to the scrambled movie," Mehta said. "This shows that the hippocampal neurons are extracting episodic information from the incoming visual information that is agnostic to the episode."

Mehta said the findings are also crucial for improving AI. "The hippocampus is at the apex of a deep neural network, with the eyes at the front end, followed by the thalamus, primary visual cortices and ending up in the hippocampus." But, given the prevailing belief that the mouse hippocampus is "the GPS system," experiments could either study the

visual cortex or the hippocampus, but not both at the same time.

"Our findings open up the possibility to study all these brain areas simultaneously and determine how the brain creates an episode from a series of images falling on the retina," Dr. Purandare said. "Selective and episodic activation of the mouse hippocampus using a human movie opens up the possibility of directly testing human episodic memory disorders and therapies using mouse neurons, a major step forward."

The study appears in the journal *eLife*.

More information: Chinmay Purandare et al, Mega-scale movie-fields in the mouse visuo-hippocampal network, *eLife* (2023). DOI: 10.7554/eLife.85069.1

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