

## 'Anxiety cells' identified in the brain's hippocampus

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**By Nicholas Weiler** [1]



"We wanted to understand where the emotional information that goes into the feeling of anxiety is encoded within the brain," said UCSF Psychiatry researcher Mazen Kheirbek, PhD [2]

Do your palms sweat when you walk down a poorly lit street at night? That feeling may be traced to the firing of newly identified 'anxiety' cells deep inside your brain, according to new research from neuroscientists at UC San Francisco and the Columbia University Irving

Medical Center (CUIMC), published online January 31, 2018 in *Neuron* [3].

The researchers found the cells in the brains of mice, inside a structure called the hippocampus. But the cells probably also exist in humans, the authors say.

## **Controlling neurons with light let scientists reduce or increase anxiety in mice**

"We call these anxiety cells because they only fire when the animals are in places that are innately frightening to them," said Rene Hen, PhD, a professor of psychiatry at CUIMC and one of the study's senior investigators. "For a mouse, that's an open area where they're more exposed to predators, or an elevated platform."

The firing of the anxiety cells sends messages to other parts of the brain that turn on anxious behaviors - in mice, those include avoiding the dangerous area or fleeing to a safe zone. Though many other cells in the brain have been identified as playing a role in anxiety, the cells found in this study are the first known to represent the state of anxiety, regardless of the type of environment that provokes the emotion.

"This is exciting because it represents a direct, rapid pathway in the brain that lets animals respond to anxiety-provoking places without needing to go through the higher-order brain regions," said Mazen Kheirbek, PhD [2], an assistant professor of psychiatry and member of the Weill Institute for Neurosciences [4] at UCSF, and study's other senior investigator.

"Now that we've found these cells in the hippocampus, it opens up new areas for exploring treatment ideas that we didn't know existed before," said the study's lead author, Jessica Jimenez, an MD/PhD student at Columbia University's Vagelos College of Physicians & Surgeons.

## **Anxiety is healthy?to a degree**

Anxiety - an emotional response to a distant threat - is normal and critical to an animal's safety. In an environment that exposes an animal to predators, for example, the safe bet is to sidestep those environments: so anxiety typically triggers avoidance behaviors. However, when people overestimate threats - when talking to a crowd invokes the same response as walking through the jungle at night -anxiety becomes a problem.

To understand how things go awry in anxiety disorders, researchers in the Hen and Kheirbek labs have been looking at mice to decipher how the brain processes healthy anxiety.

"We wanted to understand where the emotional information that goes into the feeling of anxiety is encoded within the brain," said Kheirbek.

The hippocampus plays a well-known role in the brain's ability to form new memories and to help animals-from mice to humans-navigate through complex environments. But recent research has also implicated the hippocampus in regulating mood, and studies have shown altering brain activity in the ventral part of the hippocampus can reduce anxiety. It's also known that the hippocampus sends signals to other areas of the brain-the amygdala and the hypothalamus-that have also been shown to control anxiety-related behavior.

## Anxiety cells identified with miniature microscope

Using a miniature microscope inserted into the brains of the mice, the researchers recorded the activity of hundreds of cells in the hippocampus as the mice freely moved around their surroundings.

Whenever the animals were in exposed, anxiety-provoking environments, the researchers noticed that specific cells in the ventral part of the hippocampus were active. And the more anxious the mice seemed, the greater the activity in the cells.

The researchers traced the output of those cells to the hypothalamus, which is known to control behaviors associated with anxiety (in people, those include increased heart rate, avoidance, and secretion of stress hormones).

By turning the anxiety cells off and on using a technique called optogenetics, which allows scientists to control the activity of neurons using beams of light, the researchers demonstrated that the anxiety cells control anxiety-related avoidance behaviors. When the cells were silenced, the mice spent more time wandering onto elevated platforms and away from protective walls. When the cells were stimulated, the mice exhibited more anxiety-behaviors even when they were in "safe" surroundings.

## Therapeutic directions

The discovery of the anxiety cells raises the possibility of finding treatments that target them and reduce anxiety. "We're looking to see if these cells are different molecularly from other neurons," Hen said. "If there's a specific receptor on the cells that distinguishes them from their neighbors, it may be possible to produce a new drug to reduce anxiety."

The study was supported by grants from the National Institutes of Health <sup>[5]</sup>, Intelligence Advanced Research Projects Activity <sup>[6]</sup>, Defense Advanced Research Projects Agency <sup>[7]</sup>, NY STEM awards <sup>[8]</sup>, and the Weill Scholar Award program <sup>[9]</sup>.

See paper online for full list of authors. The authors report no financial or other conflicts of interest.

## Read the study

- **Science:** Anxiety cells in a hippocampal-hypothalamic circuit <sup>[10]</sup>

## Further coverage

- **NPR:** Researchers discover 'anxiety cells' In the brain <sup>[11]</sup>
- **Forbes:** Researchers discover 'anxiety cells' in the brains of mice <sup>[12]</sup>
- **UPI:** Researchers identify 'anxiety cells' inside the brains of mice <sup>[13]</sup>

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Columbia University Irving Medical Center provides international leadership in basic,

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## **About UCSF Psychiatry**

The UCSF Department of Psychiatry [16] and the Langley Porter Psychiatric Institute are among the nation's foremost resources in the fields of child, adolescent, adult, and geriatric mental health. Together they constitute one of the largest departments in the UCSF School of Medicine and the UCSF Weill Institute for Neurosciences, with a mission focused on research (basic, translational, clinical), teaching, patient care and public service.

UCSF Psychiatry conducts its clinical, educational and research efforts at a variety of locations in Northern California, including UCSF campuses at Parnassus Heights, Mission Bay and Laurel Heights, UCSF Medical Center, UCSF Benioff Children's Hospitals, Zuckerberg San Francisco General Hospital and Trauma Center, the San Francisco VA Health Care System and UCSF Fresno.

## **About the UCSF Weill Institute for Neurosciences**

The UCSF Weill Institute for Neurosciences [17], established by the extraordinary generosity of Joan and Sanford I. "Sandy" Weill, brings together world-class researchers with top-ranked physicians to solve some of the most complex challenges in the human brain.

The UCSF Weill Institute leverages UCSF's unrivaled bench-to-bedside excellence in the neurosciences. It unites three UCSF departments—Neurology, Psychiatry, and Neurological Surgery—that are highly esteemed for both patient care and research, as well as the Neuroscience Graduate Program, a cross-disciplinary alliance of nearly 100 UCSF faculty members from 15 basic-science departments, as well as the UCSF Institute for Neurodegenerative Diseases, a multidisciplinary research center focused on finding effective treatments for Alzheimer's disease, frontotemporal dementia, Parkinson's disease, and other neurodegenerative disorders.

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UC San Francisco (UCSF) [18] is a leading university dedicated to promoting health worldwide through advanced biomedical research, graduate-level education in the life sciences and health professions, and excellence in patient care. It includes top-ranked graduate schools of dentistry, medicine, nursing and pharmacy; a graduate division with nationally renowned programs in basic, biomedical, translational and population sciences; and a preeminent biomedical research enterprise. It also includes UCSF Health, which comprises top-ranked hospitals—UCSF Medical Center [19] and UCSF Benioff Children's Hospitals in San Francisco [20] and Oakland [21]—and other partner and affiliated hospitals and healthcare providers throughout the Bay Area.

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