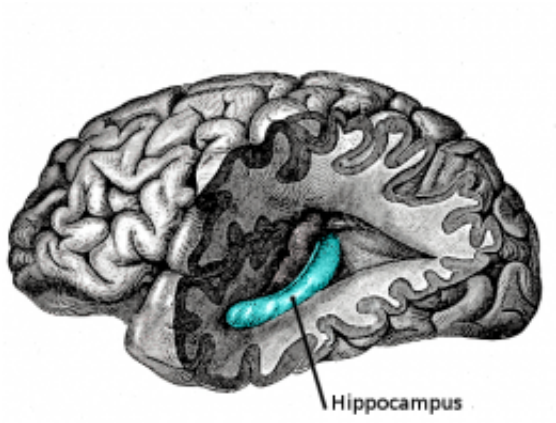
Portion of hippocampus found to play role in modulating anxiety

March 6 2013



The hippocampus is located in the medial temporal lobe of the brain. Image via Wikipedia.

Columbia University Medical Center (CUMC) researchers have found the first evidence that selective activation of the dentate gyrus, a portion of the hippocampus, can reduce anxiety without affecting learning. The findings suggest that therapies that target this brain region could be used to treat certain anxiety disorders, such as panic disorder and post-traumatic stress syndrome (PTSD), with minimal cognitive side effects. The study, conducted in mice, was published today in the online edition of the journal *Neuron*.

The dentate gyrus is known to play a key role in learning. Some evidence suggests that the structure also contributes to anxiety. "But until now no

one has been able to figure out how the hippocampus could be involved in both processes," said senior author Rene Hen, PhD, professor of neuroscience and pharmacology (in psychiatry) at CUMC.

"It turns out that different parts of the dentate gyrus have somewhat different functions, with the dorsal portion largely dedicated to learning and the ventral portion dedicated to anxiety," said lead author Mazen A. Kheirbek, PhD, a postdoctoral fellow in neuroscience at CUMC.

To examine the role of the dentate gyrus in learning and anxiety, the investigators used a state-of-the-art technique called optogenetics, in which light-sensitive proteins, or opsins, are genetically inserted into neurons in the brains of mice. Neurons with these genes can then be selectively activated or silenced through the application of light (via a fiber-optic strand), allowing researchers to study the function of the cells in real time. Previously, the only way to study the dentate gyrus was to silence portions of it using such long-term manipulations as drugs or lesions, techniques that yielded conflicting results.

In the current study, opsins were inserted into dentate gyrus granule cells (the principal cells of the dentate gyrus). The researchers then activated or silenced the ventral or dorsal portions of the dentate gyrus for three minutes at a time, while the mice were subjected to two well-validated anxiety tests (the elevated plus maze and the open field test).

"Our main findings were that elevating cell activity in the dorsal dentate gyrus increased the animals' desire to explore their environment. But this also disrupted their ability to learn. Elevating activity in the ventral dentate gyrus lowered their anxiety, but had no effect on learning," said Dr. Kheirbek. The effects were completely reversible—that is, when the stimulation was turned off, the animals returned to their previous anxiety levels.

"The therapeutic implication is that it may be possible to relieve anxiety in people with anxiety disorders by targeting the ventral dentate gyrus, perhaps with medications or deep-brain stimulation, without affecting learning," said Dr. Hen, who is also director of the Division of Integrative Neuroscience, The New York State Psychiatric Institute, and a member of The Kavli Institute for Brain Science. "Given the immediate behavioral impact of such manipulations, these strategies are likely to work faster than current treatments, such as serotonin reuptake inhibitors."

According to Dr. Hen, such an intervention would probably work best in people with panic disorder or PTSD. "There is evidence that people with these anxiety disorders tend to have a problem with pattern separation—the ability to distinguish between similar experiences," he said. "In other words, they overgeneralize, perceiving minor threats to be the same as major ones, leading to a heightened state of anxiety. Such patients could conceivably benefit from therapies that fine-tune hippocampal activity."

Dr. Hen and his team are currently exploring strategies aimed at modulating the activity of the ventral dentate gyrus by stimulating neurogenesis in the ventral dentate gyrus. "Indeed the dentate gyrus is one of the few areas in the adult brain where neurons are continuously produced, a phenomenon termed adult hippocampal neurogenesis," added Dr. Hen.

More information: The title of the paper is "Differential control of learning and anxiety along the dorso-ventral axis of the dentate gyrus."

Provided by Columbia University Medical Center