Brain recalls old memories via new pathways

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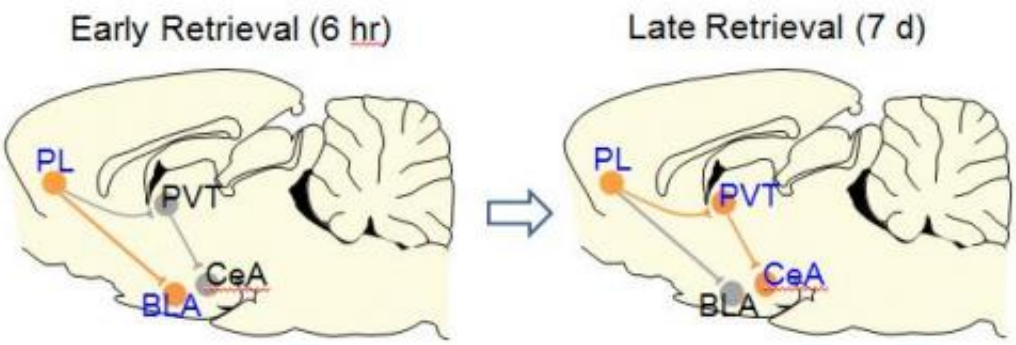

Although rats' behavior did not change over time following fear conditioning, the underlying circuitry activated to retrieve the fear memory shifted, perhaps increasing its staying power. An initial circuit from the pre-limbic prefrontal cortex to the basolateral amygdala was supplanted, a week later, by a circuit to the central amygdala via the paraventricular nucleus of the thalamus. It's thought that the paraventricular nucleus of the thalamus may serve to integrate fear with other adaptive responses. The discovery may provide clues to improved treatments for anxiety disorders. Credit: Gregory Quirk, University of Puerto Rico School of Medicine

People with anxiety disorders, such as post traumatic stress disorder (PTSD), often experience prolonged and exaggerated fearfulness. Now, an animal study suggests that this might involve disruption of a gradual shifting of brain circuitry for retrieving fear memories. Researchers funded by the National Institutes of Health have discovered in rats that an old fear memory is recalled by a separate brain pathway from the one originally used to recall it when it was fresh.

After rats were conditioned to fear a tone associated with a mild shock, their overt behavior remained unchanged over time, but the pathway engaged in remembering the traumatic event took a detour, perhaps increasing its staying power.

"While our memories feel constant across time, the neural pathways supporting them actually change with time," explained Gregory Quirk, Ph.D., of the University of Puerto Rico School of Medicine, in San Juan, a grantee of NIH's National Institute of Mental Health (NIMH). "Uncovering new pathways for old memories could change scientists' view of post-traumatic stress disorder, in which fearful events occur months or years prior to the onset of symptoms."

A research team led by Quirk and Fabricio Do-Monte, D.V.M., Ph.D., report on their findings January 19, 2015, in the journal *Nature*.

Immediately after fear conditioning, a circuit running from the prefrontal cortex, the executive hub, to part of the amygdala, the fear hub, was engaged to retrieve the memory. But several days later, Quirk and colleagues discovered that retrieval had migrated to a different circuit - from the prefrontal cortex to an area in the thalamus, called the paraventricular region (PVT). The PVT, in turn, communicates with a different central part of the amygdala that orchestrates fear learning and expression.

The Quirk team spotted the moving memory using a genetic/laser technique called optogenetics, which can activate or silence specific pathways to tease apart their workings.

The researchers say that the PVT may serve to integrate fear with other adaptive responses, such as stress, thereby strengthening the fear memory.

"In people with anxiety disorders, any disruption of timing-dependent regulation in retrieval circuits might worsen fear responses occurring long after a traumatic event," Quirk suggested.

In the same issue of *Nature*, NIMH grantees Bo Li, Ph.D., and Mario Penzo, Ph.D. of Cold Spring Harbor Laboratory in New York, and colleagues, reveal how the long-term fear memory circuit works in mice to translate detection of stress into adaptive behaviors.

Li and colleagues independently discovered the same shift in memory retrieval circuitry occurring, over time, after fear conditioning in mice. Using powerful genetic-chemical, as well as optogenetic, methods to experimentally switch pathways on and off, they showed conclusively that neurons originating in the PVT regulate fear processing by acting on a class of neurons that store fear memories in the central amygdala area.

The Li team traced this activity in the PVT to the action of a messenger chemical, brain-derived neurotrophic factor (BDNF), which has previously been implicated in mood and anxiety disorders. For example, altered BDNF expression has been linked to PTSD.

BDNF from the PVT, working via a specific receptor, activated the memory-storing amygdala neurons. Simply infusing BDNF into the central amygdala area caused mice to freeze in fear, suggesting that it not only enables the formation of fear memories, but also the expression of fear responses.

More information: Do-Monte HF, Quinones-Laracuente K, Quirk, GJ. A temporal shift in the circuits mediating retrieval of fear memory. *Nature*, Jan. 19, 2015. DOI: 10.308/nature14030

Penzo MA, Robert V, Tucciarone J, De Bundel D, Wang M, Van Aeist L, Varvas M, Parada LF, Palmiter R, He M, Huang ZJ, Li B. The

paraventricular thalamus controls a central amygdala fear circuit. *Nature*, Jan. 19, 2015. DOI: 10.1038/nature13978