From stimulus to emotion: A role for cortex in emotional learning

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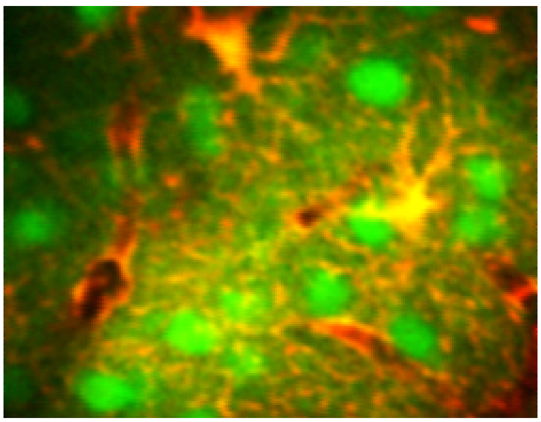

Nerve cells (green) and glia cells (orange) in the cortex.

(Medical Xpress) -- A team of neurobiologists around Andreas Lüthi at the Friedrich Miescher Institute of Biomedical Research has shown for the first time that cortex, the largest area of the brain that is typically associated with higher functions such as perception and cognition, is also a prominent site of emotional learning. Letzkus and colleagues used a set of recently developed methods to observe through which neuronal circuits activity is conveyed during learning. This study, published in Nature, demonstrates a causal link between neuronal activity patterns and animal behavior, and provides pioneering work exploring emotions in the brain.

Anxiety disorders are a family of complex diseases, which affect around

10% of adults. One of the hallmarks of these disorders is that patients have "learned" to fear situations or objects to a degree that is not proportional to the real danger. The amygdala, a structure deep in the brain, is central to the processing of fear and anxiety, and its function may be disrupted in anxiety disorders.
But, there is no fear without a sensory input: We hear, see, smell, taste or feel something that then triggers fear. These sensory signals are processed in the cortex, the region of the brain typically associated with higher functions such as perception and cognition. However, how this brain region is involved in emotional learning has hardly ever been addressed.

For the first time, scientists in the team of Andreas Lüthi, group leader at the FMI and professor at the University of Basel, have been able to follow a sensory stimulus during learning on its cellular path through the brain. Their results, describing a circuit in cortex critical for associative fear learning, have been published today in the distinguished scientific journal Nature.

Looking inside a learning brain

In Lüthi's experiments, mice learned to associate a tone with an unpleasant stimulus so that the tone itself becomes unpleasant to the animal. During this learning process the researchers visualized the activity of the neurons in the brain using 2-photon calcium imaging.

Under normal conditions, activity in neuronal networks is tightly controlled by a fine-tuned balance of synaptic excitation (which promotes firing) and synaptic inhibition (which prevents firing). Thus, any incoming signal is rapidly quenched by inhibition, allowing firing only for a very brief time after stimulus onset. In contrast, the authors found that learning opens a prolonged time window of reduced inhibition, termed 'dis-inhibition'. Thus, when the animal perceives a tone during learning, it is processed much more intensely than under normal conditions. This increased activity likely induces synaptic plasticity which underlies memory formation.

Neuronal circuit in cortex necessary for learning

Lüthi then went on to show that this dis-inhibitory microcircuit is also present in other areas of cortex, like the one processing visual input. "A really interesting aspect of our observations is that dis-inhibition appears to be necessary for learning, but does not cause learning on its own. Rather, what we perceive during a state of heightened arousal will determine what we actually learn" explains Lüthi.

To strengthen their findings further, Johannes Letzkus and Steffen Wolff, both in Lüthi's group, made use of optogenetics. They used this recently developed technique to interfere selectively with dis-inhibition during learning. When they tested the memory of these mice the next day, they found a severe impairment, which directly demonstrates that dis-inhibition is indispensable for learning.

"For the first time, thanks to the recent technological developments in modern neurobiology, we can look into the black box and actually show what happens in these neuronal circuits during associative learning on a cellular level and thereby elucidate the psychological concepts of arousal and attention in learning," said Lüthi.

More information: Letzkus JJ, Wolff SBE, Meyer EMM, Tovote P, Courtin J, Herry C, Lüthi A. (2011) A disinhibitory microcircuit for associative fear learning in auditory cortex. *Nature*, DOI: 10.1038/nature10674