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To fear or not - how does the brain switch?

Which neurons in the brain mediate fear responses - and how do they flip the switch when the danger is over? The research team of Prof. Ingrid Ehrlich at the Institute of Biomaterials and Biomolecular Systems (IBBS), Department of Neurobiology studies these questions. Their latest results obtained in collaboration with scientists at the Friedrich Miescher Institute in Basel (Switzerland), the National Institute of Health (USA), and Innsbruck Medical University (Austria) are now published in Nature und eLife.

We are all familiar with this situation: Through a bad experience we learn to fear something, that was previously not threatening. However, if the threatening situation does not persist, we learn to lose our fear. This protective mechanism normally keeps us out of harm's way. However, its dysfunction can lead to mental conditions such as anxiety-related and post-traumatic stress disorders.

Which neurons in the brain participate in this protective mechanism and how do they enable a switch in behavior? To address this questions, researchers took advantage of the fact that laboratory mice, exactly like humans, can learn by classical conditioning to fear a tone. If subsequently, the tone is not paired with an aversive experience anymore, the mice will learn to lose their fear, a process called extinction. It is known that distinct neural circuits in the brain mediate fear and extinction learning and memory. However, how these circuits interact is still incompletely understood.

For a while, the research group of Prof. Ehrlich has had its sight set on a specific group of neurons in the brain, the so-called intercalated cells. These neurons are arranged in small groups (clusters) much like a net around the amygdala, a brain region controlling fear and emotional behavior. In the Nature publication, the collaboration partners were able to show that a specific cluster of intercalated cells becomes active when the mice associate the tone with an aversive event and show a fearful reaction to the sound. When the mice learn not to fear the tone anymore, a different cluster becomes active.

"We suspected that these two clusters of intercalated cells influenced the activity of each other and that of other fear- and extinction-mediating neurons in an outside of the amygdala" Ehrlich says. "We experimentally manipulated these cells and could indeed show that the two clusters mutually inhibit each other, if one is active, it switches the other off and vice versa. One of the cell clusters emerges as the winner from this tug-of-war, and then controls fear behavior via its specific connections to downstream neurons."

A special feature of intercalated cells is that they receive dense connections from another brain area implicated in learning and memory, the dopaminergic midbrain. Dopamine-producing neurons are particularly active when something unexpected happens- this is also the case during extinction learning. The eLife publication investigated the effect of dopamine on intercalated cell clusters during extinction learning. First, the researchers made the unexpected discovery that besides dopamine, other neurotransmitters (mainly the inhibitory substance GABA) are released onto intercalated cells. Dopamine itself regulates the interaction between intercalated cell clusters. Upon extinction learning, the effect of the transmitter substances changes: The cell cluster that is more active during fear is more strongly inhibited by GABA and its inhibition on the cluster active during extinction is reduced by dopamine. "This suggests that the inputs from dopaminergic midbrain can decide the tug-of-war between the intercalated cells" suspects Ehrlich.

To unravel the complex interactions of precise neural networks in the context of learning about fear, the researchers combined several state of the art techniques in neuroscience, such as genetic manipulations, opto- and chemogenetic methods, electrophysiological recordings, in vivo imaging and neuroanatomical approaches. "Our successful collaborations in international teams were helpful and decisive" Ehrlich emphasizes.

Since intercalated neurons also exist in the human brain, these results suggest that a dysregulation of their interaction and activity balance could also play a role in neuropsychiatric disorders. Ultimately, these findings could inform novel paths for therapeutic interventions.

Originalpublikationen:

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