The rhythm of fear mapped in neuronal networks

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Researchers based in Munich and Bordeaux have detected coordinated oscillations in the activities of neuronal networks in two distinct areas of the brain, which are characteristic for a specific fear response.

The fear response evoked by traumatic or threatening situations helps us evade or escape danger. Moreover, this vital response must be learned, by forming an association between a stimulus or situation and the presence of a stressor (e.g. physical danger). This association is very powerful and leaves a memory trace that persists for years after the initial experience, generating profound structural and functional changes

in the brain that can potentially develop into post-traumatic stress and other anxiety-related disorders. LMU researchers, in collaboration with colleagues in Bordeaux, have now described a signaling mechanism - in the form of a collective oscillation in the electrical activity in two separate areas in the brain, which reflects the rhythmic firing of networks in these regions and is linked to the regulation of a particular fear behavior. The findings appear in the leading journal *Nature Neuroscience*.

Fear learning requires only a single experience for the association to be formed, and each subsequent exposure to the conditioned stimulus leads to the retrieval of the memory. Both the learning and retrieval of fear memory are characterized by a fearful fight-or-flight behavioral state, which is associated with a range of unique physiological correlates, such as sweating, tremor, and increased heart rate. The question posed by the authors at the outset of the new study was the following: Might this very characteristic physiological state perhaps represent more than just a response to the stressor or conditioned stimulus? Could it be that the fear-associated state actually reflects a characteristic activation state of the brain that facilitates learning and memory retrieval?

Decades of research have identified multiple brain regions that are involved in associative fear learning, including the dorsal medial prefrontal cortex (dmPFC) and the basolateral amygdala (BLA), both of which have emerged as structures that are critical for the learning and expression of fear. The prefrontal cortex is known to regulate cognitive functions in social behavior, while the amygdala is involved in the control of emotional states and affective behaviors. However, it was not clear up to now how the two regions communicate with each other, which neuronal mechanisms are responsible for triggering fear-related reactions such as freezing, and what functional state of the brain is correlated with such behavior.

"A self-generated symphony"

In the experiments reported in the new study teams led by Anton Sirota and Nikolaos Karalis (LMU) and Cyril Herry (Neurocentre Magendie, Bordeaux) have been able to show in an animal model, for the first time, that the overt freezing behavior is indeed correlated with a defined configuration of neural activity in the brain. The researchers first conditioned mice by exposing them to a tone which was immediately followed by a mildly aversive stimulation. The mice learned to associate the acoustic signal with the stressor, and exhibited a characteristic fear-related reaction whenever they subsequently heard the tone: They suddenly froze and remained immobile for long periods, indicating that the memory of the aversive experience was reactivated. In parallel, the researchers recorded what was going on in the mouse's brain. The overt fear reaction was found to be correlated with the appearance in the prefrontal cortex of an oscillating wave of electrical activity with a frequency of exactly four cycles per second, or 4 Hertz. Almost immediately, a similar wave of activity emerged in the amygdala. In other words, a sustained, collective oscillation couples and synchronizes neural activity in two brain areas that are remote from each other. "We have discovered what one might call a self-generated symphony in the brain," says Anton Sirota, LMU professor at the Bernstein Center for Computational Neuroscience and Synergy Cluster of Excellence. "The brain is like an orchestra that has no need for a conductor. It produces the tonal sequences and finds the rhythms appropriate to each behavior all on its own."

Oscillations have emerged as an important mechanism for the organization of collective neural activity and are implicated in both the physiological and pathological functioning of the brain. The exploratory state is associated with distinct internal dynamics known as theta (~8 Hz) oscillations, while the state of deep sleep is characterized by slow (~1 Hz) oscillations. The novel, internally generated brain state described in

the new study – characterized by 4-Hz oscillations and associated with the expression of fear – provides a new framework for the study of the neural mechanisms involved in fear memory formation, retrieval and expression. Moreover, in defining a physiological signature of fear memory within neural networks in the prefrontal cortex and the basal region of the amygdala, the results suggest that blocking oscillations in this circuit might represent a potential therapeutic strategy for pathological conditions such as anxiety disorders.

More information: Nikolaos Karalis et al. 4-Hz oscillations synchronize prefrontal–amygdala circuits during fear behavior, *Nature Neuroscience* (2016). DOI: 10.1038/nn.4251

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