Fearful memories of pain stored in the prefrontal cortex could shape the experience of pain later in life

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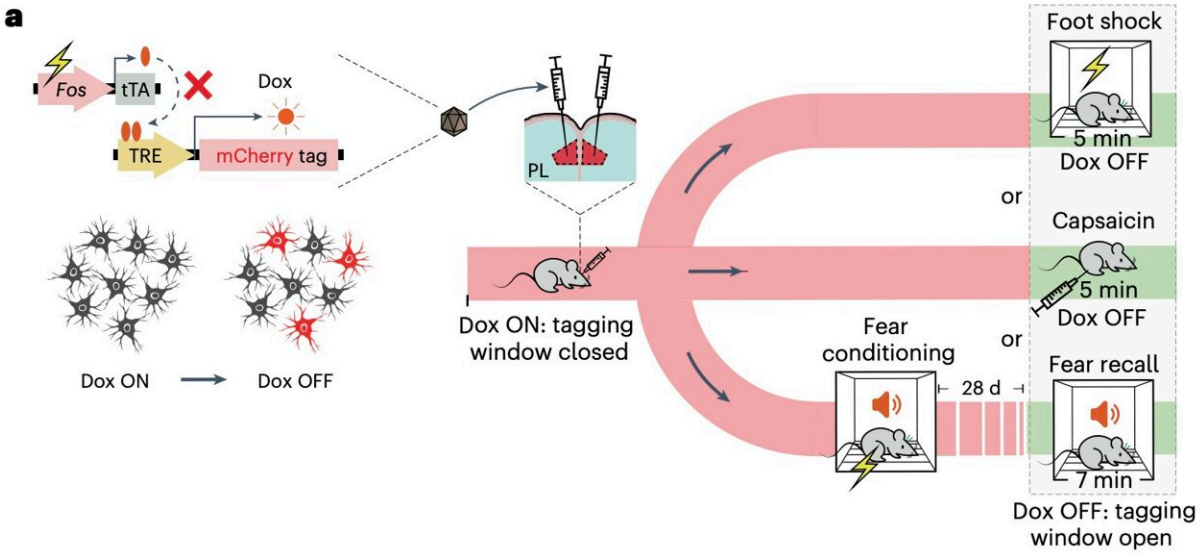

Viral-mediated, Dox-controlled expression of protein tags under the Fos promoter, leading to activity-dependent tagging of prelimbic neurons with mCherry following painful foot shock or capsaicin or during recall of fear memory 28 d after cued fear conditioning. Credit: Stegemann et al

While pain and fear are very different experiences, past studies showed that they can sometimes be closely related to one another. For instance, when many animals and humans are in dangerous or life-threatening

situations, acute fear can suppress their perception of pain, allowing them to fully focus their attention on what is happening to them.

Conversely, research showed that when humans experience high levels of pain, they can create long-term and associative fear memories that make them fearful of situations that they associate with the pain they felt. These memories can in turn increase their sensitivity to pain or lead to the development of unhelpful behavioral patterns aimed at avoiding pain.

The increase in the intensity with which animals or humans perceive pain after very painful past experiences could be liked to their fearful anticipation of pain. The exact neural underpinnings of this process, however, are still poorly understood.

Researchers at Heidelberg University have recently carried out a study aimed at better understanding which regions of the mice brain stores very painful experiences and how these stored memories can affect future experiences of pain. Their findings, published in *Nature Neuroscience*, suggest that these memories are stored in the prefrontal cortex, the area covering the front part of the mammalian brain.

The researchers conducted a series of experiments on adult mice using a neural tagging method and optogenetic techniques. During these experiments, the mice received small electric shocks on their feet and were conditioned to become fearful of receiving these shocks again. The team also used optogenetic techniques to either activate or suppress different neural circuits in the mice's brain, to determine how this would affect their sensitivity to pain.

"We show in mice that long-term associative fear memory stored in neuronal engrams in the prefrontal cortex determines whether a painful episode shapes pain experience later in life," Alina Stegemann, Sheng

Liu and their colleagues wrote in their paper.

"Furthermore, under conditions of inflammatory and neuropathic pain, prefrontal fear engrams expand to encompass neurons representing nociception and tactile sensation, leading to pronounced changes in prefrontal connectivity to fear-relevant brain areas. Conversely, silencing prefrontal fear engrams reverses chronically established hyperalgesia and allodynia."

The recent work by this team of researchers outlines some of the neural mechanisms that could play a role in the perpetuation of pain over long periods of time resulting from the formation of fearful associative memories of past pain. Their findings could potentially inspire the development of new therapeutic interventions for chronic pain manifestations that can be linked to previous painful experiences. These therapeutic interventions could, for instance, combine cognitive behavioral therapy with drugs targeting neural circuits in the prefrontal cortex.

"These results reveal that a discrete subset of prefrontal cortex neurons can account for the debilitating comorbidity of fear and chronic pain and show that attenuating the fear memory of pain can alleviate chronic pain itself," Stegemann, Liu and their colleagues wrote in their paper. "Our study provides causal evidence for diminishing pathological pain by overpowering anticipatory fear and gives an impetus for developing interventions targeting prefrontal circuitry in individuals with chronic pain and comorbid fear."

More information: Alina Stegemann et al, Prefrontal engrams of long-term fear memory perpetuate pain perception, *Nature Neuroscience* (2023). DOI: 10.1038/s41593-023-01291-x