Visualization and modulation of ensembles in the hippocampus and amygdala during fear reinstatement

Post-traumatic stress disorder (PTSD) is a condition that precipitates from a highly aversive experience and is manifested by overgeneralized fear in innocuous situations. Interestingly, a striking proportion of patients who undergo exposure therapy - which can lead to the suppression, or “extinction,” of the original fear memory - are highly vulnerable to relapse. Here, we interrogated the neural substrates supporting the acquisition of fear, the subsequent extinction of fear, and relapse. We used activity-dependent labeling of neuronal ensembles in multiple brain regions associated with fear-related behaviors (basolateral amygdala, BLA; dorsal dentate gyrus of hippocampus, dDG) and further manipulated these ensembles using optogenetics to probe the changes that a fear memory undergoes during extinction and during fear reinstatement.

We tagged BLA or dDG cells processing a contextual fear memory in mice. Mice then underwent extinction learning, and we inhibited the tagged fear ensemble either during a shock in an unconditioned context (to reinitiate the original context-specific fear) or during a fear recall test in the original conditioned context the day after. We found that while inhibition of the original fear ensemble in the BLA was not enough to prevent reinstatement, inhibition of the fear ensemble in both regions during the recall test was enough to actively disrupt fear expression in the conditioned context. Using calcium imaging, we found that population similarity to the cellular activity during FC decreased across EXT in both the CA1 and the BLA, but then increased after reinstatement, during recall. These results suggest a re-emergence of the original fear ensemble during fear reinstatement.

Abstract

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We tagged BLA or dDG cells processing a contextual fear memory in mice. Mice then underwent extinction learning, and we inhibited the tagged fear ensemble either during a shock in an unconditioned context (to reinitiate the original context-specific fear) or during a fear recall test in the original conditioned context the day after. We found that while inhibition of the original fear ensemble in the BLA was not enough to prevent reinstatement, inhibition of the fear ensemble in both regions during the recall test was enough to actively disrupt fear expression in the conditioned context. Using calcium imaging, we found that population similarity to the cellular activity during FC decreased across EXT in both the CA1 and the BLA, but then increased after reinstatement, during recall. These results suggest a re-emergence of the original fear ensemble during fear reinstatement.

Activity-Dependent Labeling and Manipulation of Neuronal Ensembles

Inhibiting Fear Ensemble to Prevent or Suppress Reinstatement-Induced Fear

Can inhibition of the original fear ensemble in the BLA prevent acquisition of reinstatement-induced fear?

Inhibition of Fear Ensemble During Reinstatement Does Not Affect Recall

Inhibition of the original fear ensemble did not prevent increase in freezing during reinstatement test following reinstating shock.

Reactive Assembly of Hippocampal and Amygdalar Fear Ensembles

In progress

The original fear ensemble was preferentially reactivated once the subject was placed back in the conditioned context the day following the reinstating shock.

Inhibitions of Fear Ensemble Disrupts Fear Following Reinstatement

• Inhibition of original fear ensemble during recall test actively mitigates freezing response.
• The original fear ensemble continues to contribute to freezing behavior following reinstating shock.

Conclusions

• Ensembles in the dDG and BLA associated with FC are reactivated during post-reinstatement recall.
• Inhibition of dDG and BLA fear ensembles during post-reinstatement recall suppresses fear response.
• The CA1 and BLA networks transform over EXT, but revert to the FC state after reinstatement.

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Acknowledgements

• Patric Davis, Laron Reimers

Collaborators: Howard Eisenbaum, Shewa Josselyn, Joshua Sanes

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We thank the support of the NSF GRC Brain and Behavioral Sciences, Ludwig Family Foundation, Elion Family Foundation, and ChildSaver, as well as grants awarded to the Broad Institute of MIT and Harvard from the National Institute of Mental Health (EY014881) and Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative (1UH3TR000714-01).