Fear extinction

- The impact of adolescent drinking on traumatic brain injury-induced cognitive deficits and alcohol preference in adult C57BL/6J mice
- Sex differences in long-term fear and anxiety-like responses to deep brain stimulation in a preclinical model of PTSD
- PACAP associated with precise PTSD and fear extinction response in women
- Cpeb1 remodels cell type-specific translational program to promote fear extinction
- CircSATB2 modulates fear extinction memory via Robo3-driven synaptic plasticity
- The interaction of Synapsin 2a and Synaptogyrin-3 regulates fear extinction in mice
- Restoring the Function of Thalamocortical Circuit Through Correcting Thalamic Kv3.2 Channelopathy Normalizes Fear Extinction Impairments in a PTSD Mouse Model
- Fear extinction is regulated by the activity of long noncoding RNAs at the synapse

Fear extinction is a psychological process that involves the reduction and eventual elimination of a learned fear response. It occurs when a person or animal learns to suppress or “extinguish” a fear response to a stimulus that was previously associated with a threat but is no longer dangerous. This process is a crucial part of adaptive learning and helps individuals cope with changing environments.

Breakdown of the fear extinction process

Learning Fear:

Initially, an individual learns to associate a specific stimulus (like a certain situation, object, or sound) with a fearful or aversive experience. This association triggers a fear response.

Exposure to Safe Environment:

Through repeated exposure to the stimulus in a safe environment (where no harm occurs), the individual starts to learn that the stimulus is no longer a threat.

Extinction Training:

Fear extinction often involves intentional exposure to the feared stimulus in a safe and controlled setting. This is known as extinction training. During this process, the individual is exposed to the fear-inducing stimulus without any harmful consequences.

Reduction of Fear Response:

With repeated and safe exposure, the fear response gradually decreases. The brain learns to inhibit the fear reaction that was previously associated with the stimulus.

Formation of New Associations:

Simultaneously, the brain may form new associations with the stimulus, associating it with safety rather than danger. Fear extinction is a form of learning that occurs in the brain, particularly in areas like the amygdala, which is strongly involved in processing emotions, including fear. The process is not about erasing the original fear memory but rather forming new associations that suppress the fear response.

Understanding fear extinction is essential in various contexts, such as treating anxiety disorders and post-traumatic stress disorder (PTSD). Therapeutic approaches often involve exposure therapy, where individuals gradually confront and overcome their fears in a controlled and supportive environment, facilitating the extinction of the fear response.

Long noncoding RNAs (lncRNAs) represent a multidimensional class of regulatory molecules that are involved in many aspects of brain function. Emerging evidence indicates that lncRNAs are localized to the synapse; however, a direct role for their activity in this subcellular compartment in memory formation has yet to be demonstrated. Using lncRNA capture-seq, Liau et al. identified a specific set of lncRNAs that accumulate in the synaptic compartment within the infralimbic prefrontal cortex of adult male C57/Bl6 mice. Among these was a splice variant related to the stress-associated lncRNA, Gas5. RNA immunoprecipitation followed by mass spectrometry and single-molecule imaging revealed that this Gas5 isoform, in association with the RNA binding proteins G3BP2 and CAPRIN1, regulates the activity-dependent trafficking and clustering of RNA granules. In addition, they found that cell-type-specific, activity-dependent, and synapse-specific knockdown of the Gas5 variant led to impaired fear extinction memory. These findings identify a new mechanism of fear extinction that involves the dynamic interaction between local lncRNA activity and RNA condensates in the synaptic compartment [1)].

A cell type- and synapse-specific, and state-dependent, reduction of m6A on Malat1 impairs fear-extinction memory; an effect that likely occurs through a disruption in the interaction between Malat1 and DPYSL2 and an associated decrease in dendritic spine formation. These findings highlight the critical role of m6A in regulating the functional state of RNA during the consolidation of fear-extinction memory, and expand the repertoire of experience-dependent m6A readers in the synaptic compartment.SIGNIFICANCE STATEMENT We have discovered that learning-induced m6A-modified RNA (including the long noncoding RNA, Malat1) accumulates in the synaptic compartment. We have identified several new m6A readers that are associated with fear extinction learning and demonstrate a causal relationship between m6A-modified Malat1 and the formation of fear-extinction memory. These findings highlight the role of m6A in regulating the functional state of an RNA during memory formation and expand the repertoire of experience-dependent m6A readers in the synaptic compartment [2)].

The dentate gyrus (DG) of the hippocampus encodes contextual information associated with fear, and cell activity in the DG is required for acquisition and extinction of contextual fear. However, the underlying molecular mechanisms are not fully understood. Here we show that mice deficient for peroxisome proliferator-activated receptor-α (PPARα) exhibited a slower rate of contextual fear extinction. Furthermore, selective deletion of PPARα in the DG attenuated, while activation of PPARα in the DG by local infusion of aspirin facilitated extinction of contextual fear. The intrinsic excitability of DG granule neurons was reduced by PPARα deficiency but increased by activation of PPARα with aspirin. Using RNA-Seq transcriptome we found that the transcription level of neuropeptide S receptor 1 (Npsr1) was tightly correlated with PPARα activation. Our results provide evidence that PPARα plays an important role in regulating DG neuronal excitability and contextual fear extinction [3)]

1)

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Zajaczkowski EL, Leighton LJ, Ren H, Musgrove M, Davies J, Rauch S, He C, Dickinson BC, Li X, Wei W, Meunier FA, Fernández-Moya SM, Kiebler MA, Srinivasan B, Banerjee S, Clark M, Spitale RC, Bredy TW. Fear extinction is regulated by the activity of long noncoding RNAs at the synapse. Nat Commun. 2023 Nov 22;14(1):7616. doi: 10.1038/s41467-023-43535-1. PMID: 37993455.
2)

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3)

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