Reactivating hippocampus-mediated memories to disrupt the reconsolidation of fear

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Abstract
Memory is thought to be stored in the brain as an ensemble of cells activated during learning, and these ensembles are thought to be reactivated during memory retrieval1,2. Reactivation of a stored memory in the brain can render the memory temporarily labile, thus susceptible to modification allowing for subsequent bidirectional manipulation (e.g. enhancement / disruption). This is referred to as reconsolidation3. The memory is then re-stabilized (reconsolidated) in a similar manner to how it was initially consolidated (e.g. correlates of long term memory). Fear conditioning has been used to model memory and stress-related behaviours in rodents22,23. While fear is often adaptive, dysregulation of fear circuits can lead to maladaptive states comprising mood and anxiety disorders24. A promising prospect of attenuating the strength of fear memories is through the disruption of reconsolidation. Previously, interventions such as protein synthesis blockers have been used to target and disrupt conditioned fear during the reconsolidation window25,27. Here, we propose a novel intervention based on the hypothesis that artificial reactivation of a previously formed, hippocampus-mediated memory during reconsolidation using optogenetics, will alter (disrupt) the original fear memory, thereby reducing the behavioural expression of fear.

Method & Experimental Design

• Inducible and activity-dependent, doxycycline (DOX)-controlled, neuronal tagging system
• Injections of an adenovirus-associated virus targeted to dorsal dentate gyrus (dDG)
• Mice express a tetracycline transactivator (TAT) driven by the c-fos promoter, encoding the light sensitive opsin, channelrhodopsin-2 (ChR2) under control of tetracycline response element (TRE)

Activity-Dependent Tagging of Positive, Neutral and Negative Memories

- Male c57BL/6 mice
- Following neuronal tagging mice were fear-conditioned (1.5mA, 2s, 4 shocks) and given a 20-min recall session the next day
- To reactivate dDG-mediated memories:
  - During recall, we optically stimulated (450nm, 20Hz) the dDG during the first or last 10min of the session
- Mice then received two 30-min extinction sessions and were tested for stress-induced reinstatement (following an immediate shock in a different context) on subsequent days

Reactivation of a Positive, Neutral, or Negative Memory Resulted in Faster Rates of Extinction

- Only occurred when optical stimulation was given during the first 10 min and was independent of valence

Reactivating a Hippocampus-Mediated Memory During Reconsolidation Prevented Reinstatement

- Reactivation of a hippocampus-mediated memory during reconsolidation prevented reinstatement

Conclusions & Future Directions

- Our results argue reactivation of a competing neutral memory alone is not sufficient to interfere with memory retrieval unless it is associated with a positive experience. We showed that reactivation of a dDG-mediated memory can accelerate extinction and attenuate reinstatement irrespective of valence.
- Our effects were stronger when manipulations occurred within the first ten minutes of the fear memory recall session: are we engaging reconsolidation mechanisms, or inducing a priming effect. When we increase the valence of the tagged experience or activate cells in the dDG until a memory our effects are enhanced. A logical explanation for our results mechanistically, involves increased interference, consistent with a role for the DG in pattern separation.
  - Spontaneous recovery (to assess how enduring the effects are)
  - Overlaps (to assess if the mechanism by which these effects occur involves an intermingling of the tagged memory and the fear memory which would argue that we are interfering with the original fear memory). Dual memory tagging (fear memory as well as tagged dDG-mediated memories) could also be theoretically used to assess whether degradation of the fear memory occurs following these manipulations
- Operate responding for positive memory (dDG-CHR2-TRE-CAMKII-tta-eYFP) reactivation and for non-specific (CAMKII-ChR2-eYFP) stimulation in the dDG
- Our findings provide preliminary evidence for the potential therapeutic efficacy of artificially modulating memories to suppress fear responses.

References

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