Artificially enhancing or suppressing hippocampus-mediated fear memories

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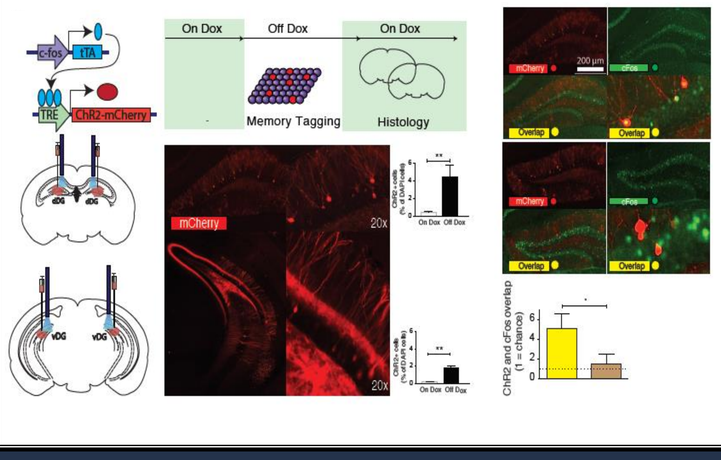
Introduction

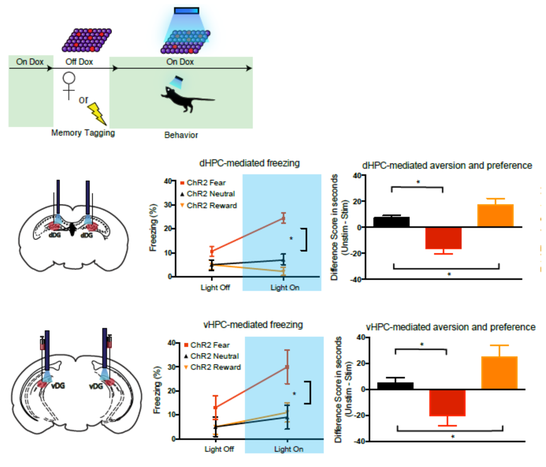
- Cognitive and emotional disruptions underlie many stress-related disorders
- The hippocampus processes cognitive and emotional aspects of learning along its dorsal-ventral extent and functional changes along this axis may differentially contribute to cognitive and emotional impairments
- Here, we asked if artificially activating a positive or negative memory in the dorsal or ventral hippocampus can promote appetitive or aversive-related behaviors
- We also examined the behavioral effects of chronic reactivation of a negative memory on fear behavior and the necessity of BLA involvement during chronic activation of the dorsal hippocampus.

Method

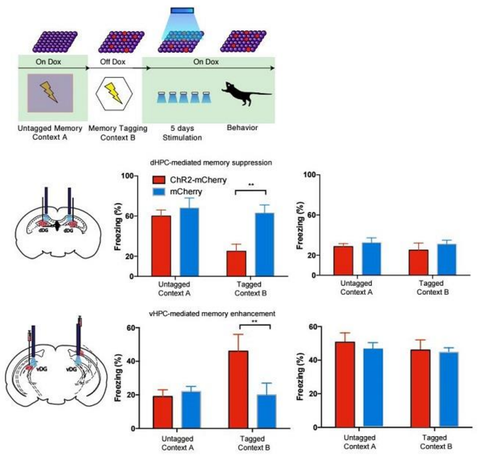
- We infused AAV9-cFos-tTA and AAV9-TRE-ChR2-mCherry or AAV9-TRE-mCherry into the dorsal (dDG) or ventral dentate gyrus (vDG) and implanted optic fibers above the injection site
- When mice are off doxycycline (Dox) diet, neuronal activation (via c-Fos) promotes the transcription of ChR2, allowing for targeting of cell ensembles active during positive or negative memory formation
- Tagged cell ensembles can then be reactivated via light-stimulation (i.e., ChR2) or CNO (hM4Di)



Bi-directional Control Over Positive and Negative Memories

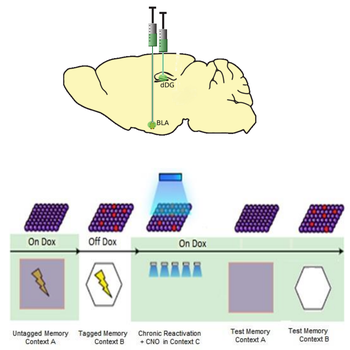


Dorsal and ventral hippocampus cells support preference and avoidance behaviors

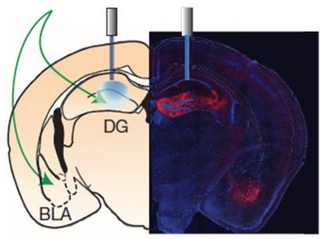


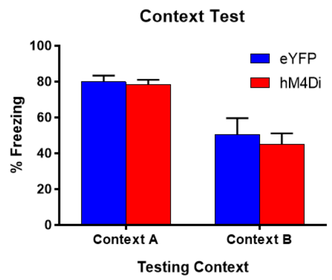
Chronic activation of negative memories is sufficient to bi-directionally modulate fear behavior

BLA Silencing During Chronic dDG Activation of Negative Memories



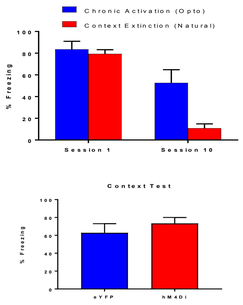
dDG: AAV-cFos-tTA-TRE-ChR2-mCherry
BLA: AAV-cFos-tTA-TRE-hM4Di-mCherry





Inactivation of tagged BLA cells during chronic dorsal hippocampus activation does not prevent context-specific extinction-like fear behavior

Additional Data



Comparison of freezing during 1st and 10th session of chronic activation (opto) and natural extinction (natural)

CNO does not disrupt context retrieval in mice with hM4Di targeted in the BLA

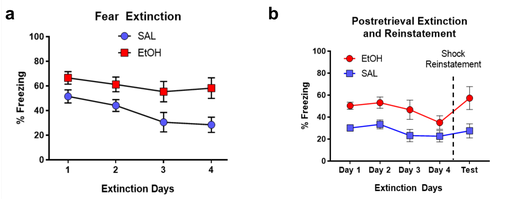
Next Steps

- vDG eYFP/c-Fos overlap to examine context specificity
- vDG chronic activation of positive, negative, or neutral memories
- dDG chronic activation of + or / effects
- BLA chronic activation

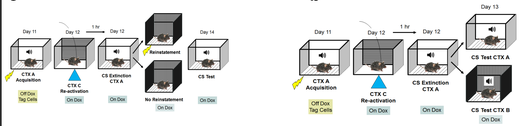
Conclusions

- Activation of dorsal and ventral hippocampus cells were sufficient to drive freezing, avoidance, and preference
- The ventral, but not dorsal, hippocampus is sufficient to modulate anxiety-like states
- Chronic activation of the dorsal hippocampus cells produces extinction-like reductions in fear responses, whereas ventral hippocampus stimulation induces a context-specific enhancement of a fear memory

Future Directions



Withdrawal from chronic EtOH impairs fear extinction (a) and increases reinstatement (b).



We will examine if optogenetic reactivation of a fear memory prior to extinction facilitates extinction and mitigates renewal (c) and reinstatement (d) in EtOH mice

Acknowledgements

This work was supported by NIH DP5, NARSAD, Harvard Milton Fund, & The Ludwig Family Foundation, and the Center for Memory and Brain at BU. Thanks to the labs of Howard Eichenbaum and Joshua Sanes for assistance.

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