Visualization and Modulation of Memories During Voluntary Aerobic Exercise

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Abstract

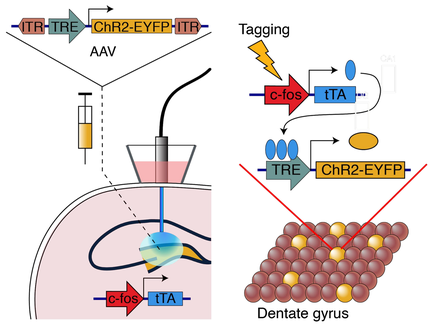
Aerobic exercise improves physical health as well as various aspects of cognition. However, the underlying circuitry mediating interactions between an episodic or emotional memory and voluntary aerobic exercise remains unclear.

Here, we selectively label cells within the dentate gyrus (DG) that are preferentially activated during the encoding of a negative memory. We next developed a closed-loop optogenetic strategy in which reactivation of a DG-mediated negative memory occurred specifically during bouts of running to test for potential real-time changes in behavior, as well as suppression or enhancement-like effects on subsequent fear memory expression.

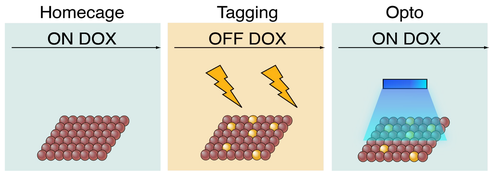
Our preliminary data suggest that optogenetically reactivating a DG-mediated negative memory has mild effects on active escape-related behavior and subsequent fear extinction and reinstatement when compared to controls. Interestingly, the ensemble within the DG that was previously active during the encoding of a negative memory does not become preferentially reactivated during bouts of voluntary exercise without optogenetic stimulation. Conversely, BLA cells previously activate during the formation of negative memories become preferentially reactivated during bouts of voluntary exercise, suggesting that BLA cells processing fear may become preferentially engaged during such behavior. Future optogenetic experiments in the BLA may reveal a putative neuronal and behavioral interaction between discrete memory-related processes and aerobic exercise.

Methods

Activity-dependent labeling of DG cells

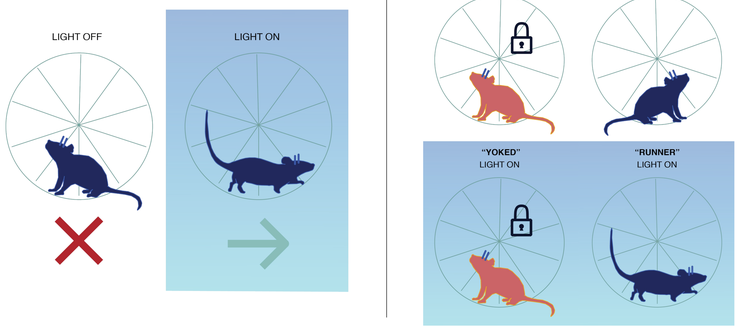


- Tetracycline transactivator (**tTA**) binds to tetracycline response element (**TRE**), leading to expression of **ChR2** only in active (***cFos*$^+$**) cells.
- Doxycycline creates a open/closed system in time for labeling.
- DG cells active during the formation of a particular episodic memory become ChR2$^+$ and can be manipulated by blue light.

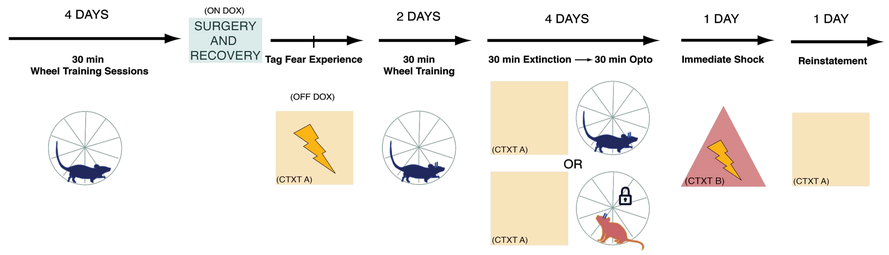


Figures adapted from Liu *et al.* 2012

Closed-loop optogenetic stimulation during voluntary aerobic exercise

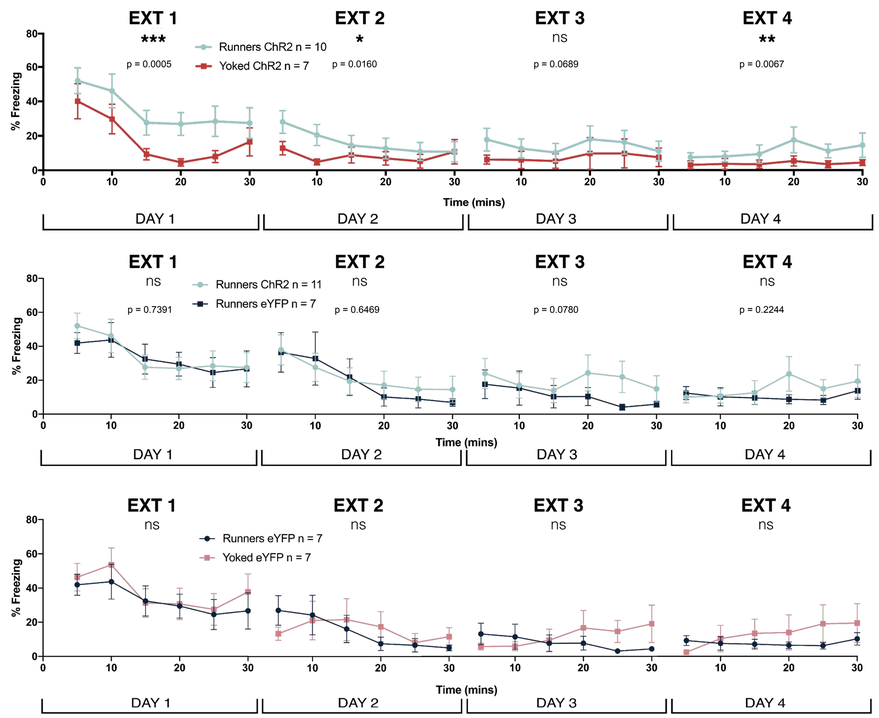


Experimental Design

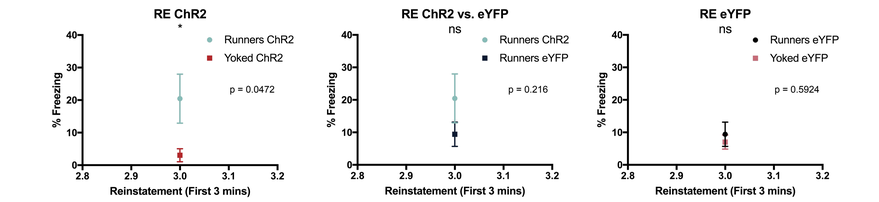


Behavior Data

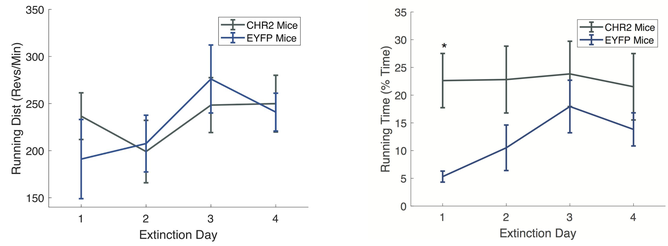
Stimulation during running has minimal effects on fear extinction learning



Stimulation during running moderately enhances reinstatement of fear



Activating DG cells alters running behavior

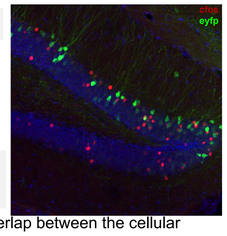


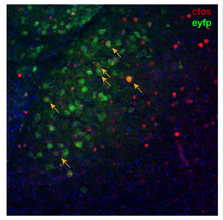
- Across four days, we observe a steady-state effect in the amount of time ChR2 mice were running.
- The amount of distance ran on EXT day 1 is significantly higher in ChR2 mice than eYFP controls, suggesting an increase in active escape-like behaviors.

Labeling and Overlap in the DG and BLA

DG shows lack of overlap

- Cells tagged during fear experience (eYFP) vs. cells that are active during aerobic exercise (cFos)
- No overlap between ensembles suggests different contextual representations





BLA cells may show overlap with fear ensemble

- Preliminary data suggests increased overlap between the cellular ensemble coding for a fear experience and the ensemble for a running experience in the BLA
- The observed overlap suggests similar emotional valence associated with both a fearful experience (i.e. foot shocks) and an experience in the running chamber.

Conclusions and Future Directions

- Closed-loop optogenetic stimulation has mild effects on fear extinction. However, ChR2 runners are not behaviorally different from eYFP runners over the course of four extinction trials.
- ChR2 runners show enhanced reinstatement in comparison to ChR2 sedentary animals.
- ChR2 runners spent more time running than eYFP runner controls. This could be attributed to an active avoidance-like behavior as a result of stimulation during bouts of running.
- Future experiments will show the effects of closed-loop optogenetic stimulation of the BLA. We additionally aim to examine the effects of reactivating cells implicated in positive memories during voluntary aerobic exercise.
- We performed these experiments in young adult male mice. Future experiments in females will elucidate possible sex differences in these behaviors.

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