Normal aging impairs extinction learning

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Introduction

Normal aging is accompanied by a loss of cognitive flexibility along with impairments in memory formation and accuracy (Perlmutter et al., 1987) and protein accumulation in the brain (Trask et al., 2020).

In Pavlovian extinction, a conditional stimulus (CS) that was previously paired with an aversive unconditional stimulus (US) is presented alone.

Extinction training results in new inhibitory (e.g., CS-No US) learning that competes with the original memory for expression (Trask et al., 2017).

Extinction may therefore rely on cognitive flexibility to adapt to changing contingencies.

This present study aims to investigate the impact that normal aging has on extinction learning following Pavlovian fear conditioning as well as protein accumulation in memory-related brain regions, including the hippocampus (Kjelstrup et al., 2002) and the retrosplenial cortex (Kwapis et al., 2015).

We predict that aging will be accompanied by impaired extinction learning and protein accumulation in the hippocampus and the retrosplenial cortex.

Materials and Methods

Subjects. Subjects were male and female young (3-month-old) and aged (20-month-old) Long Evans rats.

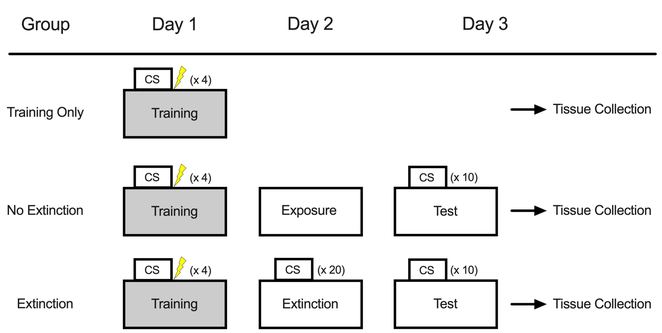
Apparatus. Behavioral procedures occurred in two sets of Colbourn conditioning chambers that were individually housed in sound attenuating cubicles. Each set was in a separate room. Training occurred in one set (Context A) and Extinction/Exposure and Testing occurred in a second set (Context B). Contexts were differentiated by tactile, visual, and olfactory cues as in our prior work to create two distinct environments (Bonanno et al., 2023).

Training. Subjects were presented with four CS-US pairings. The CS was a 10-s white noise and the US was a 1-s 1.0 mA footshock.

Exposure or Extinction. Animals in the Exposure group were placed into the chambers with no CS presentations. Animals in the Extinction group experienced 20 30-s CS presentations.

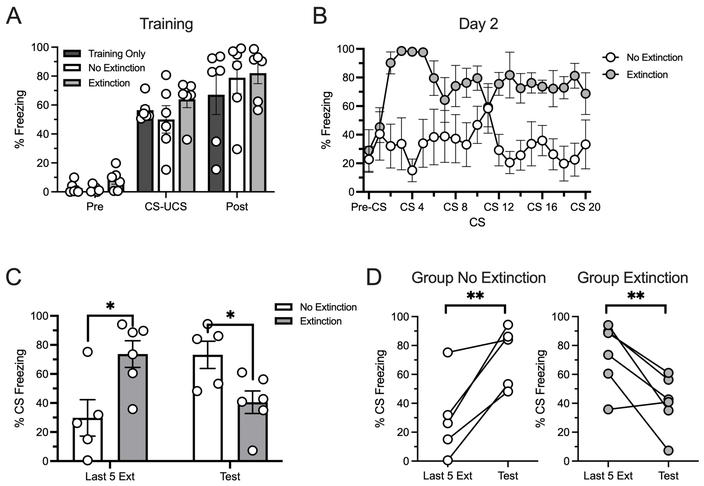
Testing. Freezing behavior was measured during 10 30-s CS presentations.

Tissue collection. Animals were sacrificed 60-minutes following behavioral testing. Subjects were deeply anesthetized with isoflurane and brains were collected and flash frozen. Tissue was collected for immunofluorescence and probed for EGR-1/zif268.

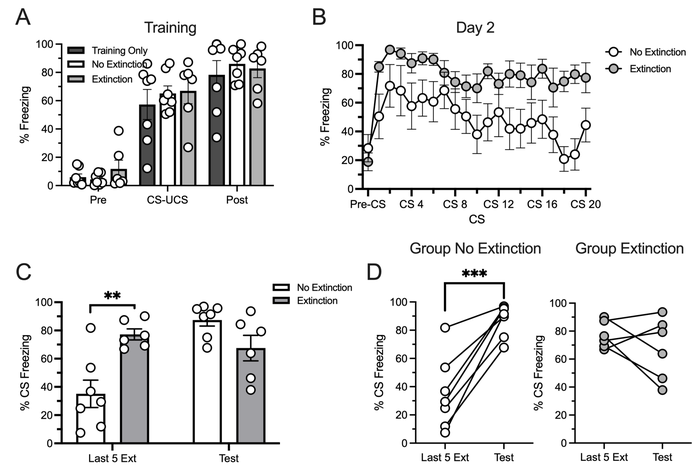


Results

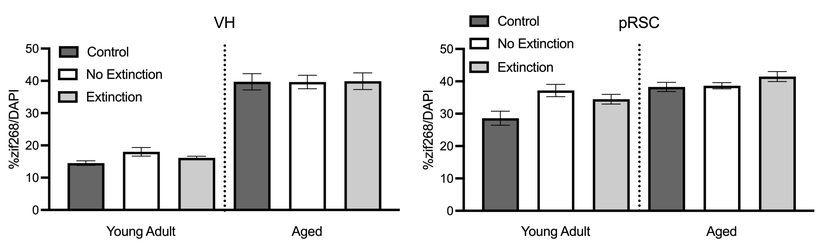
Young animals show decreased CS-elicited freezing following extinction.



Aged animals did not show a decrease in CS-elicited freezing following extinction.



zif268 expression following testing shows different patterns in young and aged animals, who show overall higher levels of the zif268 protein.



Conclusions

Young adult animals decreased their freezing behavior following extinction, suggesting they can flexibly gauge their responding when environmental contingencies changes.

Aged animals did not, reflective of reduced cognitive flexibility with age.

In young animals, high fear in the no extinction group was associated with increased zif268 in the VH and this was reduced following extinction. Both extinction and no extinction groups showed increased zif268 in the pRSC.

In both the VH and the pRSC, we see a high accumulation of the zif268 protein in the aged animals relative to the young adult animals. This accumulation has been linked to dysfunction in the ubiquitin proteasome system (Trask et al., 2020) and likely reduces normal function within these regions.

Ongoing work is assessing proteolytic function in these animals, as well as protein accumulation in other regions important for fear learning (e.g., basolateral amygdala) and cognitive flexibility (e.g., medial prefrontal cortex).

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