Generalization and discrimination of inhibitory avoidance differentially engage subregions of the retrosplenial cortex.

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Introduction

While fear responding is normally context specific (e.g., Bonanno et al., 2023), several factors can lead to a generalized fear response where behavior is no longer constrained to the acquisition context (Wiltgen & Silva, 2007; Zhou & Riccio, 1996).

Here, we examined changes in neural activity (including expression of the immediate early gene zif268 and perineuronal nets) corresponding with generalization of inhibitory avoidance.

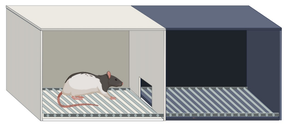
Methods

Subjects: Age matched (~3-month) male and female Long Evans rats.

Behavioral Procedure:

Training

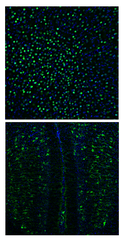
Testing



Experimental Design:

	Group	Shock Intensity	Training	Testing
How does training with a weak shock affect zif268 expression and PNN amount?	No Training Mild Shock Mild Shock	- 0.7 mA 0.7 mA	- Light Dark	- - -
How does training with a strong shock affect zif268 expression and PNN amount?	No Training Strong Shock Strong Shock	- 1.5 mA 1.5 mA	- Light Dark	- - -
How does memory retrieval following inhibitory avoidance training affect zif268 expression and PNN amount?	No Test No Test Light/Light Dark/Light Dark/Dark Light/Dark	1.5 mA 1.5 mA 1.5 mA 1.5 mA 1.5 mA 1.5 mA	Light Dark Light Dark Dark Light	- - Light Light Dark Dark

Tissue was collected 65 minutes following training or testing (depending on the experiment). Following tissue collection, we measured:

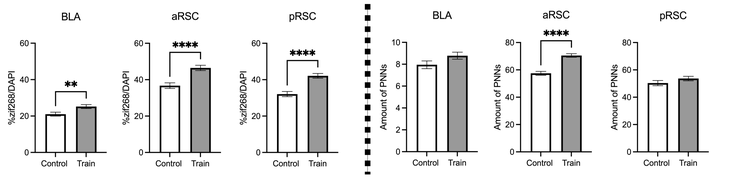


Zif268 (green) expression in the aRSC (20X magnification).

PNNs (green) in the aRSC (10X magnification).

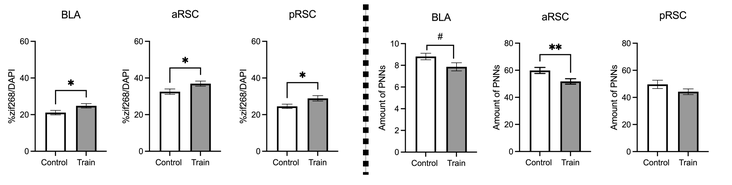
Results

Training with a weak shock (0.7 mA) increases zif268 activity in the BLA, aRSC, and pRSC. There are no corresponding decreases in PNNs.



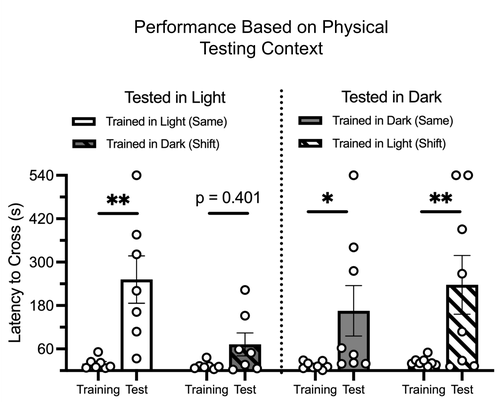
**** $p < 0.0001$ from control, ** $p < 0.01$ from control

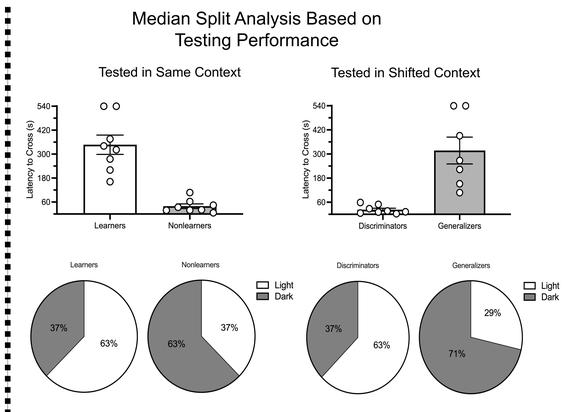
Training with a strong shock (1.5 mA) increases zif268 activity in the BLA, aRSC, and pRSC. This reduced PNNs in the aRSC and BLA.



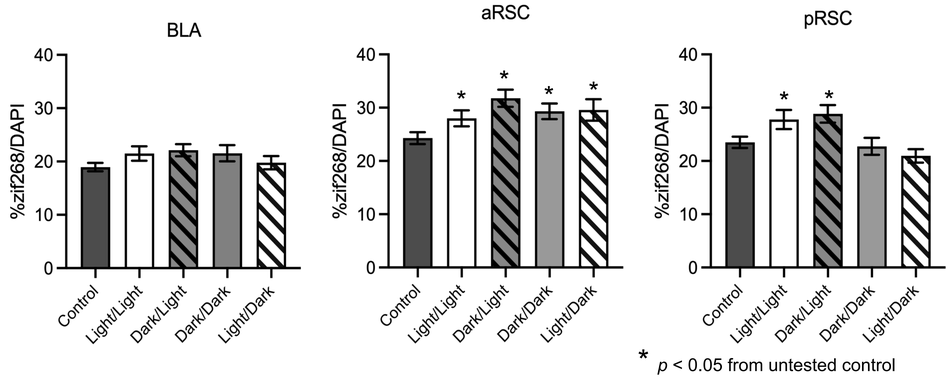
# $p < 0.10$ from control, ** $p < 0.01$ from control, * $p < 0.05$ from control

Animals tested in the light maintained context-specificity and animals tested in the dark generalized avoidance behavior.



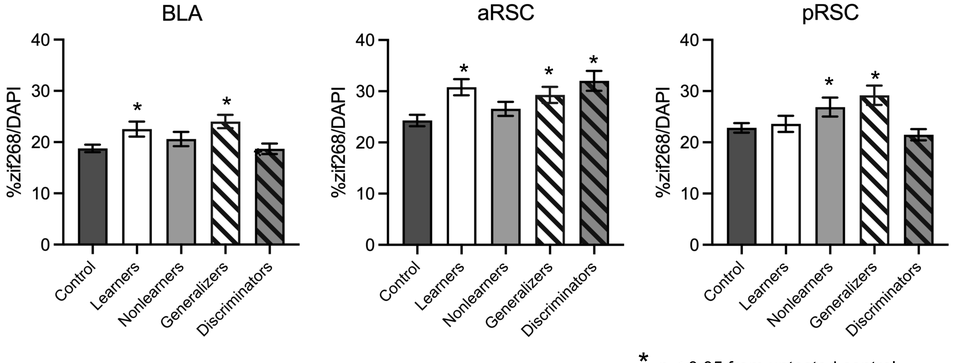


Zif268 is generally elevated in the aRSC in tested animals, but zif268 expression is only elevated in the pRSC in animals tested in the light.



* $p < 0.05$ from untested control

While BLA activity corresponds with overall levels of avoidance behavior, aRSC activity corresponds with learning and pRSC corresponds with generalization.



* $p < 0.05$ from untested control

Conclusions

Inhibitory avoidance training with both weak and strong shocks increases zif268 activity in the BLA and RSC. Animals trained with a strong shock showed a reduced amount of PNNs, in line with prior work showing PNN degradation with memory formation (Carulli et al., 2020).

We found elevated levels of zif268 activity in the BLA corresponded with higher levels of avoidance: only learners and generalizers showed increased activity. While discriminators and learners exhibited elevated levels of zif268 in the aRSC, only generalizers and nonlearners showed elevated zif268 activity in the pRSC. This suggests differential contributions of the retrosplenial cortex to specific and generalized memories.

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References

Bonanno, G. R., Met Hoxha, E., Robinson, P. K., Ferrara, N. C., & Trask, S. (2023). Fear reduced through unconditional stimulus deflation is behaviorally distinct from extinction and differentially engages the amygdala. *Biological Psychiatry Global Open Science*.

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Wiltgen, B. J., & Silva, A. J. (2007). Memory for context becomes less specific with time. *Learning & Memory*, *14*, 313-317.

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