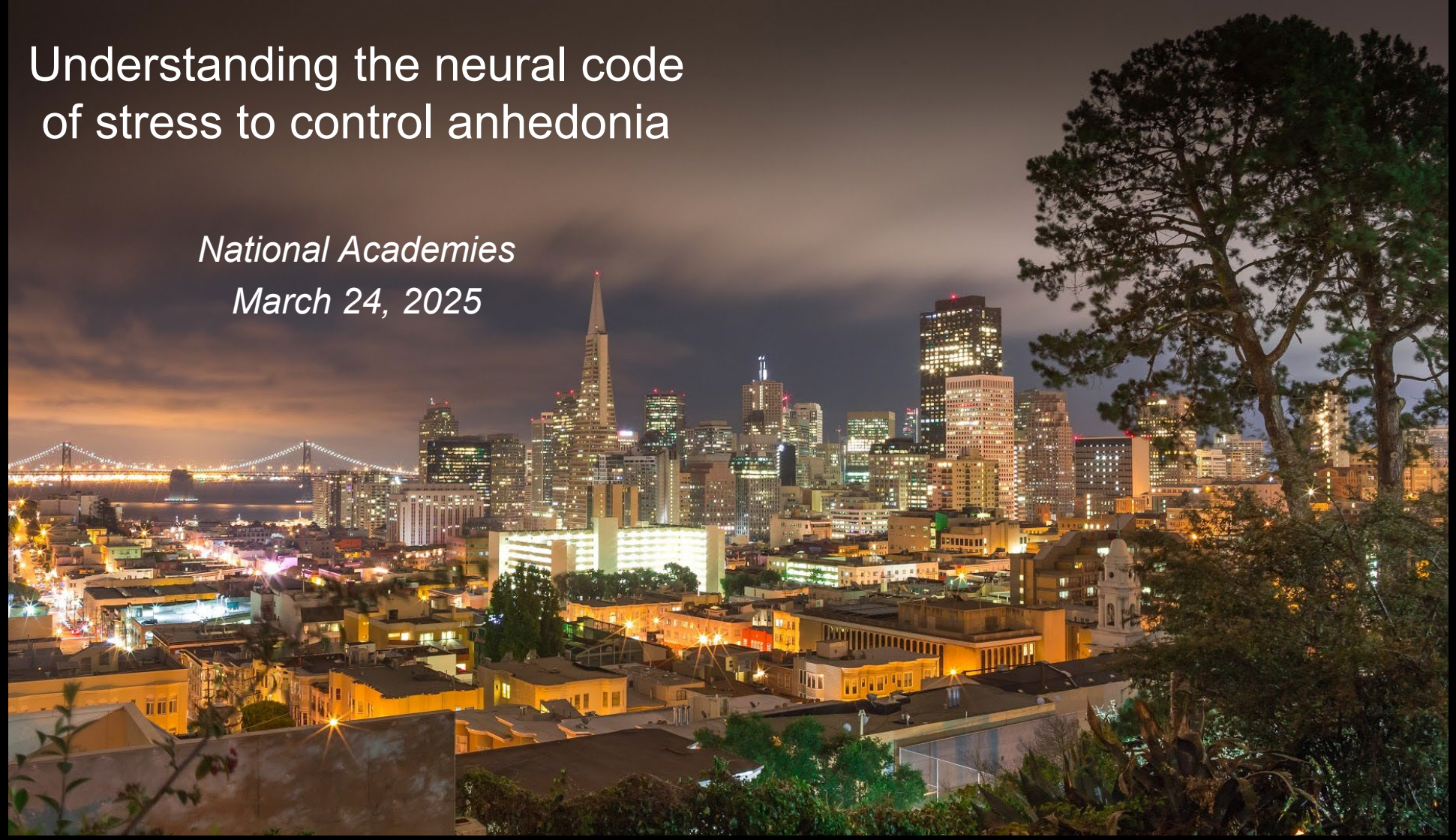
Understanding the neural code of stress to control anhedonia

National Academies

March 24, 2025



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Can we decode internal emotional states?

Can neural population dynamics explain individual differences in stress responses?

Can they predict stress resiliency or susceptibility?

Frances Xia
collaborators Valeria Fascianelli and Stefano Fusi

Amygdala-hippocampal network in mood

Cell

Article

An Amygdala-Hippocampus Subnetwork that Encodes Variation in Human Mood

Lowry A. Kirkby,[1,2,3,4] Francisco J. Luongo,[1,2,3] Morgan B. Lee,[2,3,5] Mor Nahum,[6] Thomas M. Van Vleet,[6] Vikram R. Rao,[7] Heather E. Dawes,[2,3,5] Edward F. Chang,[2,3,5,8,9,*] and Vikaas S. Sohal[1,2,3,4,8,9,10,*]

the interaction between amygdala and hippocampus is correlated with subjective mood state and can predict individual differences in mood

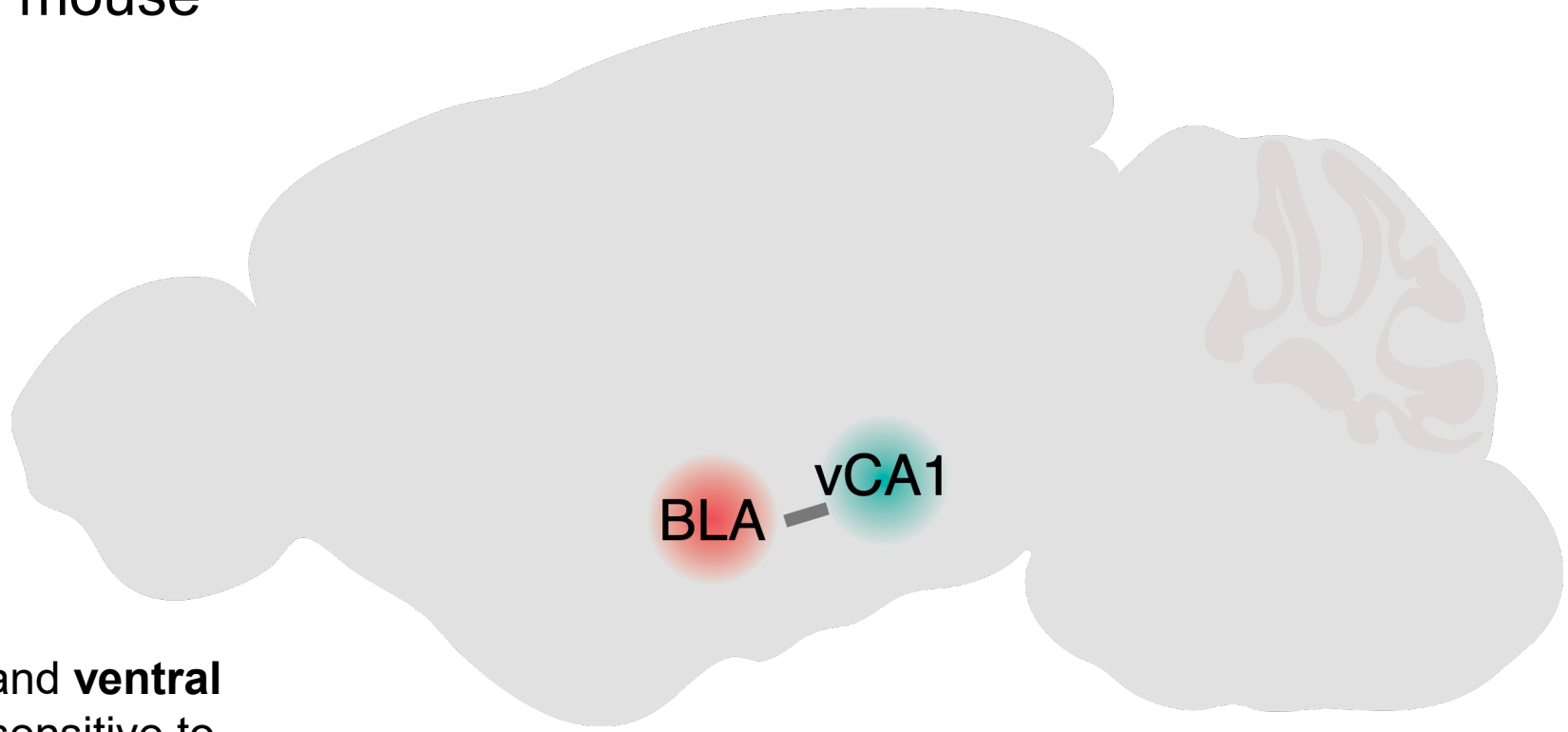
BRIEF COMMUNICATION
https://doi.org/10.1038/s41591-021-01480-w
nature medicine
Check for updates

Closed-loop neuromodulation in an individual with treatment-resistant depression

Katherine W. Scangos[1,2]✉, Ankit N. Khambhati[1,3], Patrick M. Daly[1,2], Ghassan S. Makhoul[1,2], Leo P. Sugrue[1,4], Hashem Zamanian[1,2], Tony X. Liu[1,2], Vikram R. Rao[1,5], Kristin K. Sellers[1,3], Heather E. Dawes[1,3], Philip A. Starr[1,3], Andrew D. Krystal[1,2,6] and Edward F. Chang[1,3,6]

Amygdala activity predicts depression symptom severity.
Closed loop deep brain stimulation triggered on biomarker could improve mood.

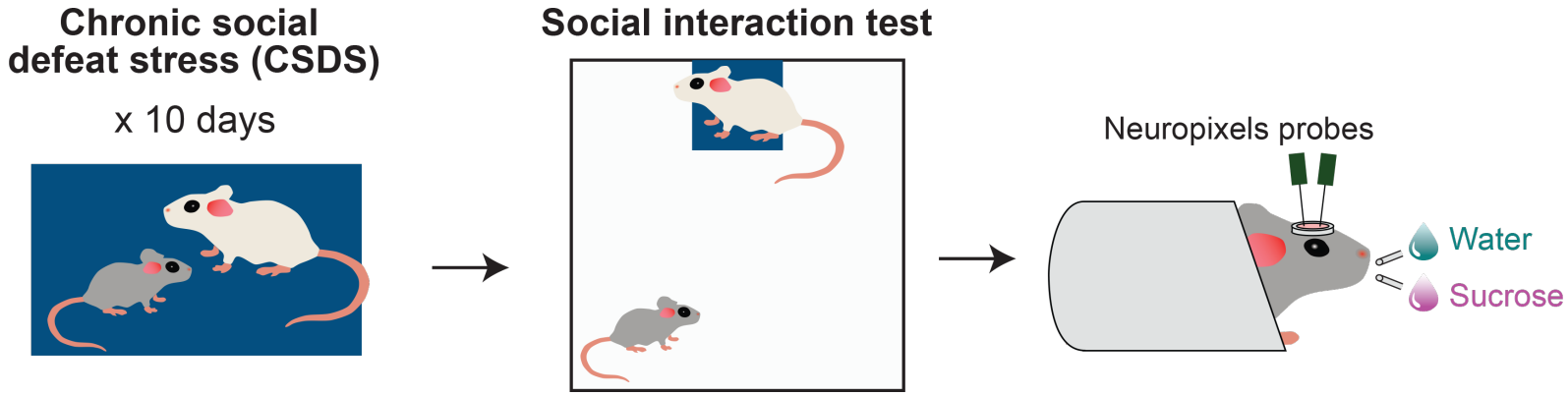
Reverse translation to the mouse

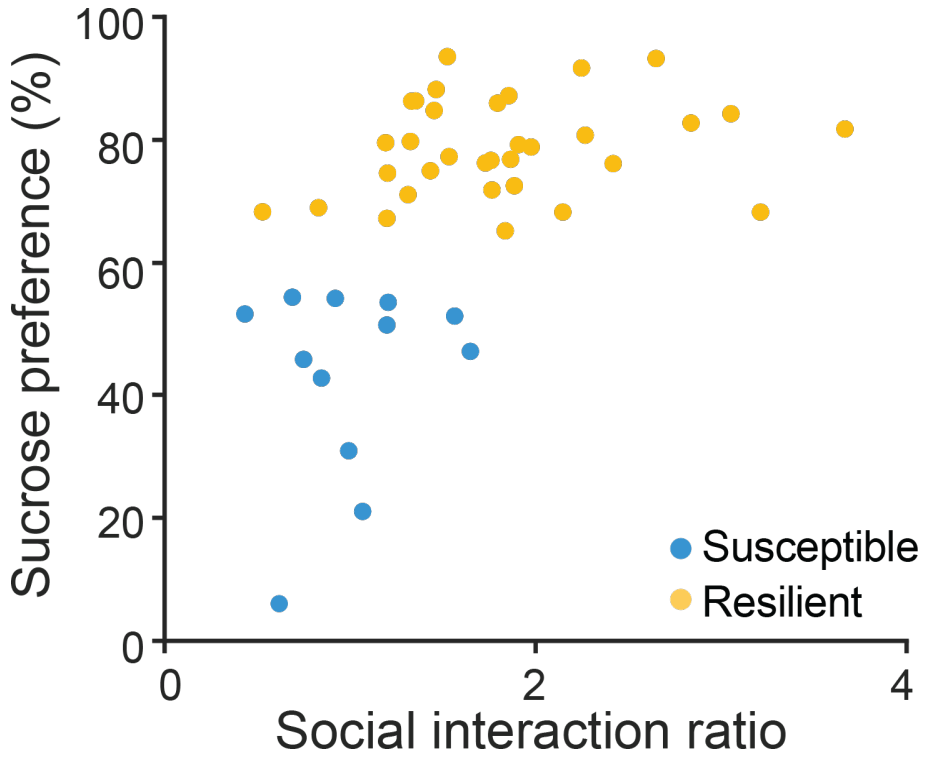


- **Basolateral amygdala (BLA)** and **ventral hippocampal CA1 (vCA1)** are sensitive to stress and encode reward information.
- Modulating activity in this network influences anxiety- and mood-related behavior

Kheirbek et al., 2013, Bagot et al., 2015, Ciocchi et al., 2015, Parfitt et al., 2017, Riaz et al., 2017, Anacker et al., 2018, Jimenez et al., 2018, LeGates et al., 2018, Gergues et al., 2020, Tye et al., 2011, Felix-Ortiz et al., 2013, 2016, Adhikari et al., 2015, Bagot et al., 2015, Beyeler et al., 2016, Hultman et al., 2018, Kirkby et al., 2018, Grundemann et al., 2019, Courtin et al., 2022, Wassum, 2022, Park et al., 2021, Shpokayte et al., 2022 Biane et al., 2023 and many others….

Classification of mice as susceptible and resilient





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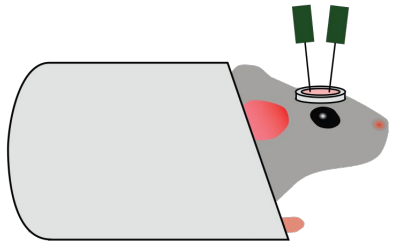
Does spontaneous, resting activity in the BLA differ in stress susceptible mice?

Chronic social defeat stress (CSDS)

x 10 days

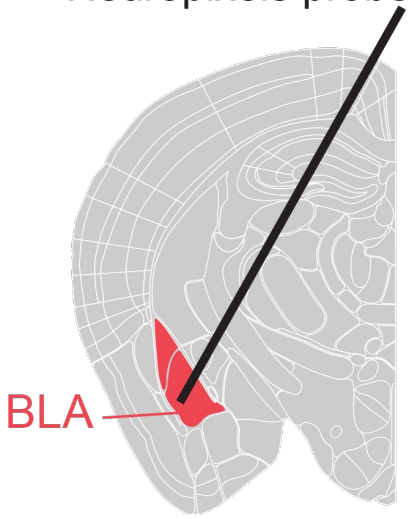
Neuropixels recordings

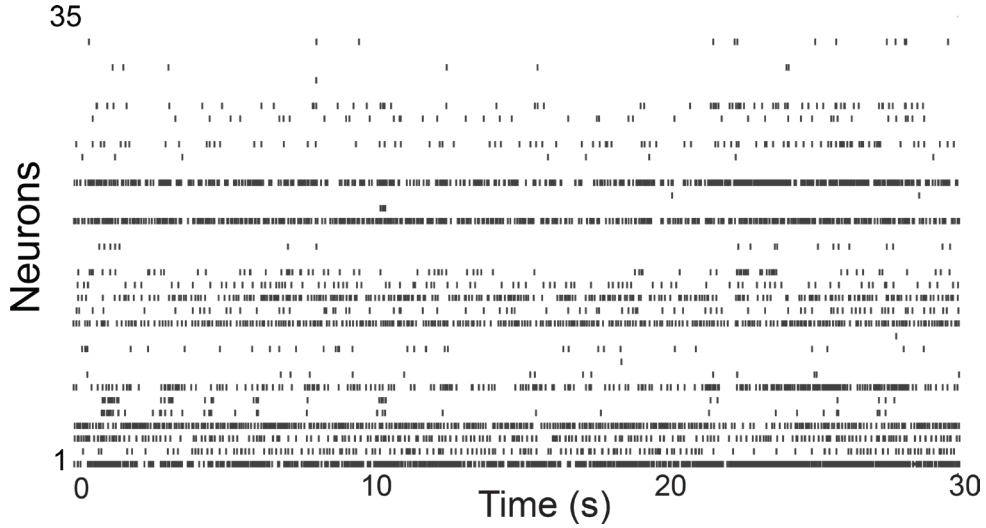


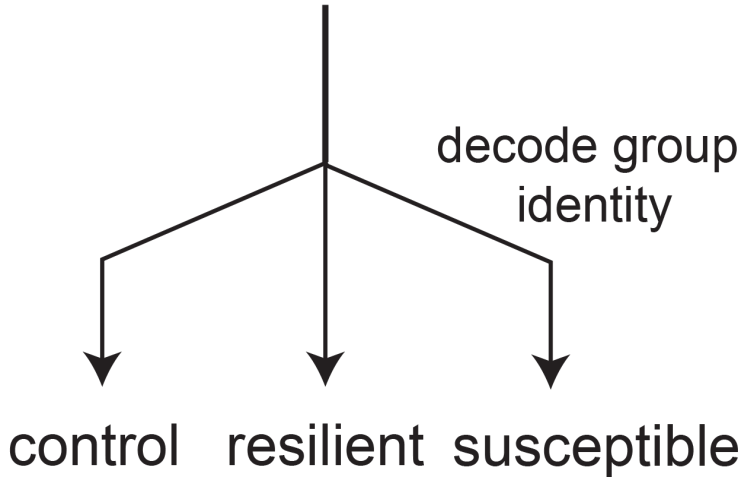
resting activity, no stimuli or tasks

6min

Neuropixels probe







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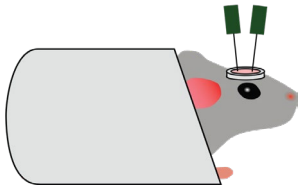
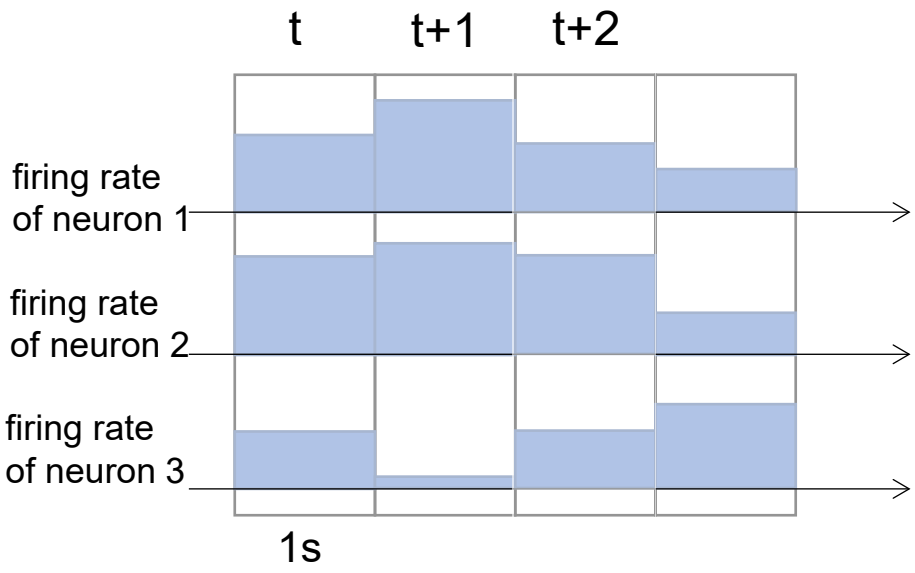
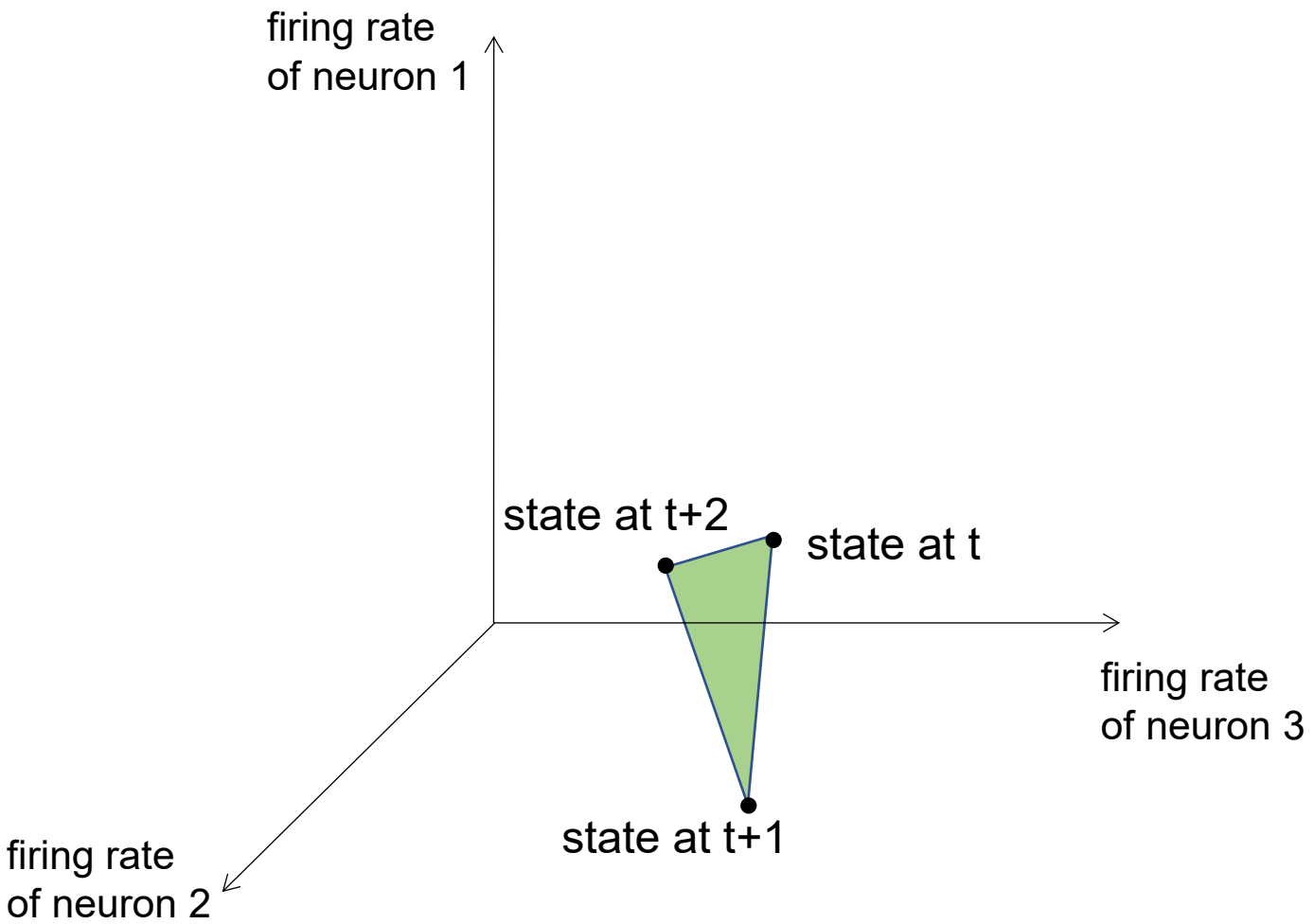
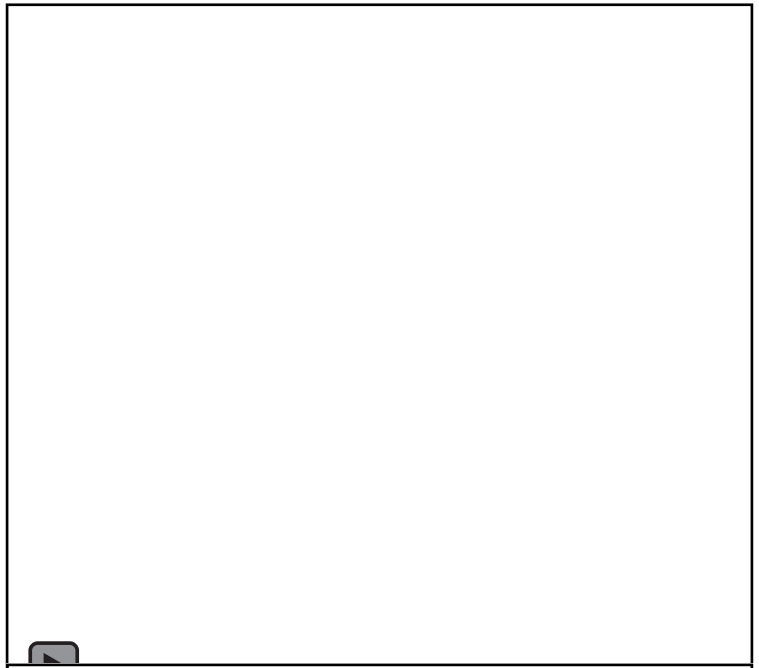
Measuring distinct states of neural population activity

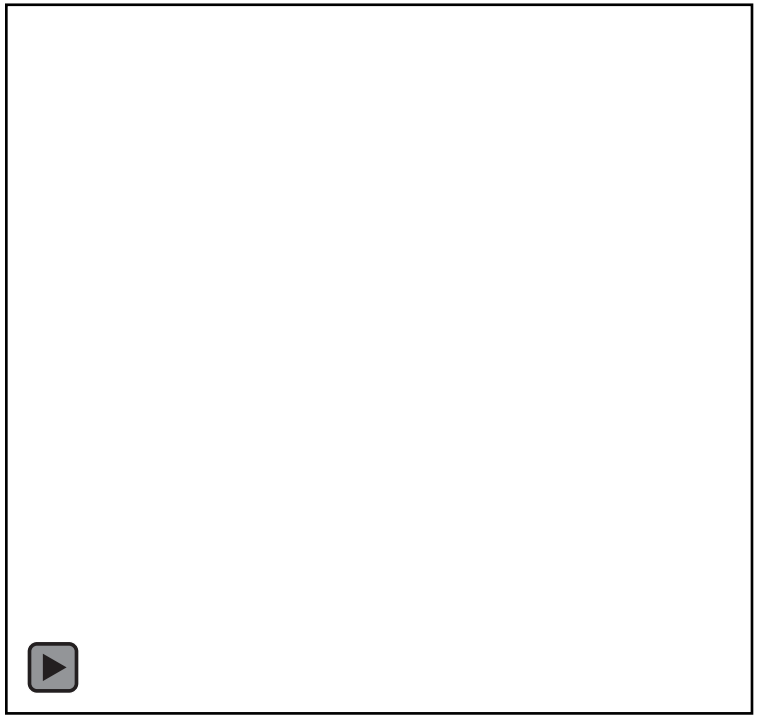
Neuropixels recordings

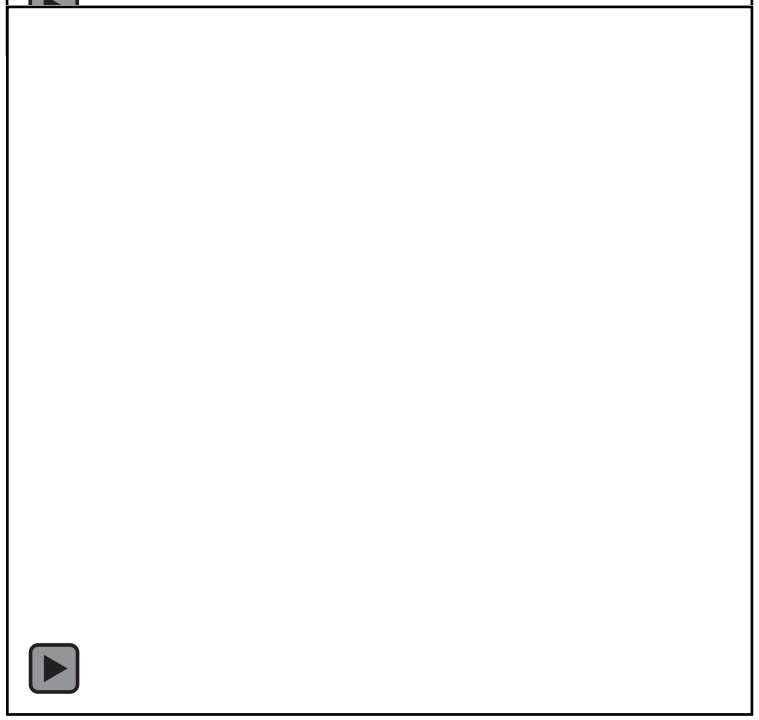






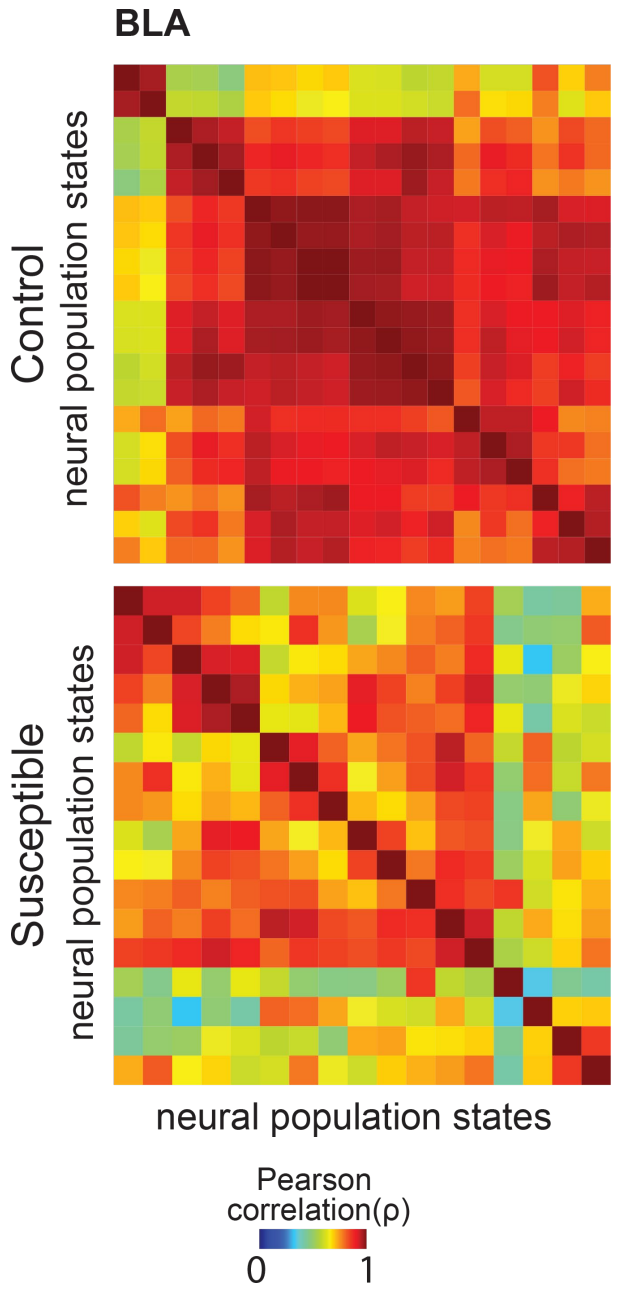


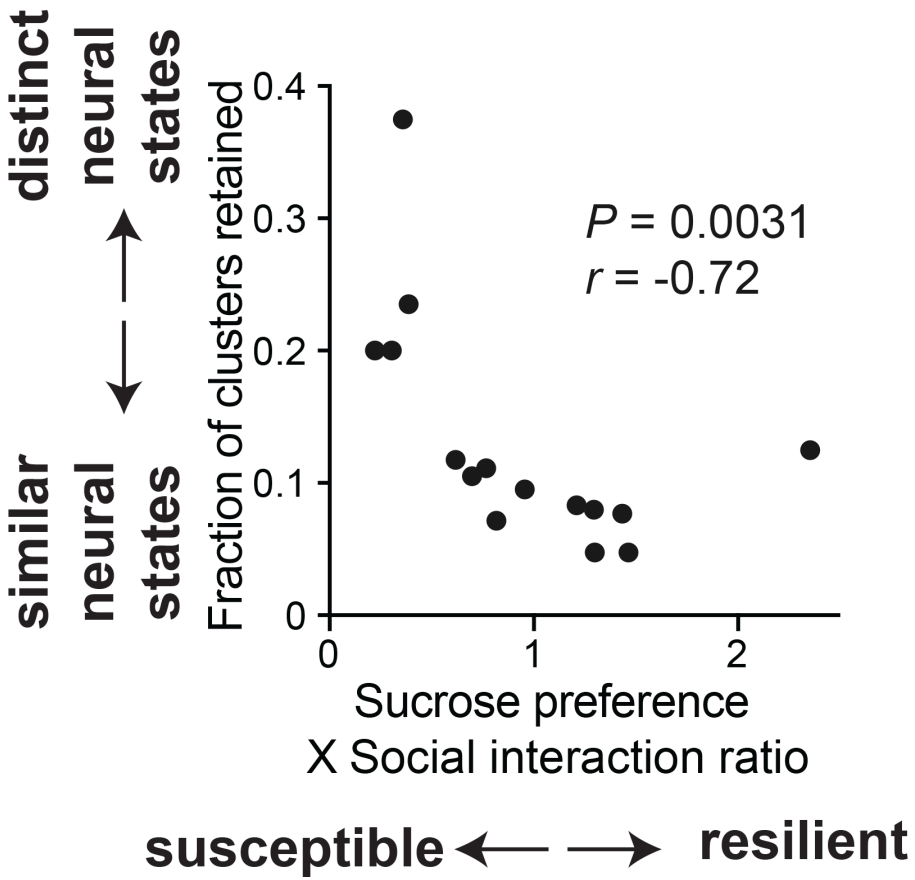


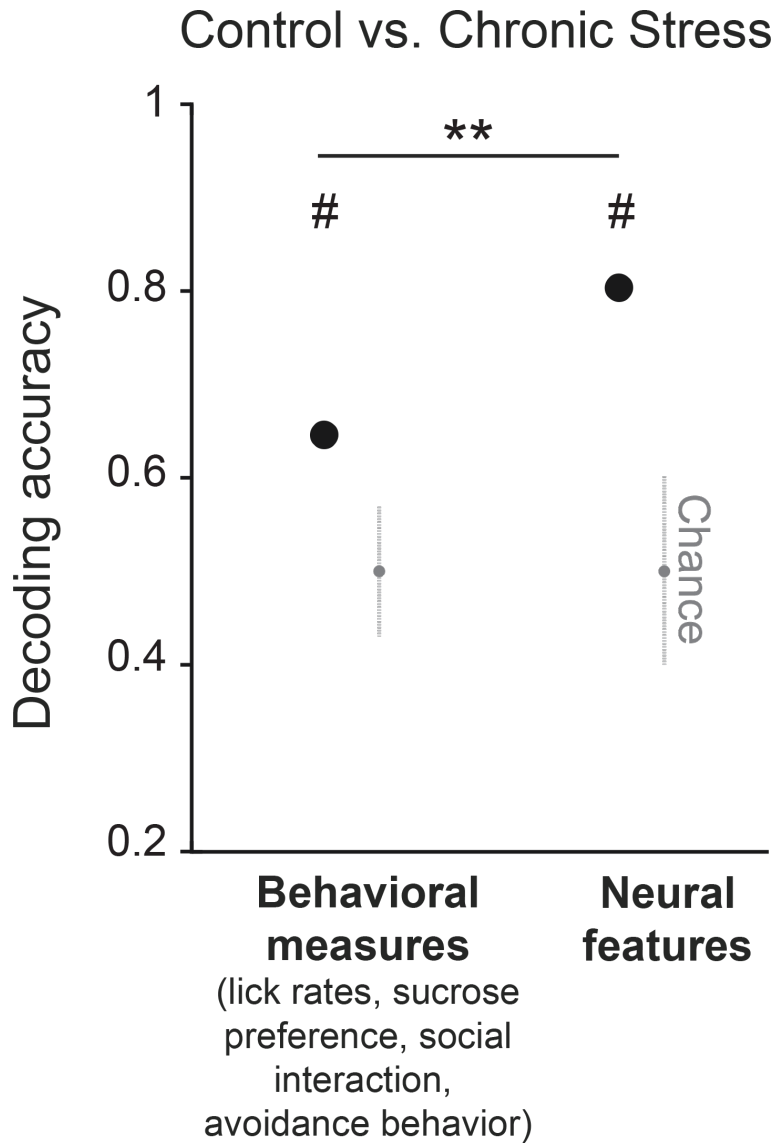


Overall, susceptible mice have **a greater number of distinct population states** than control and resilient mice.

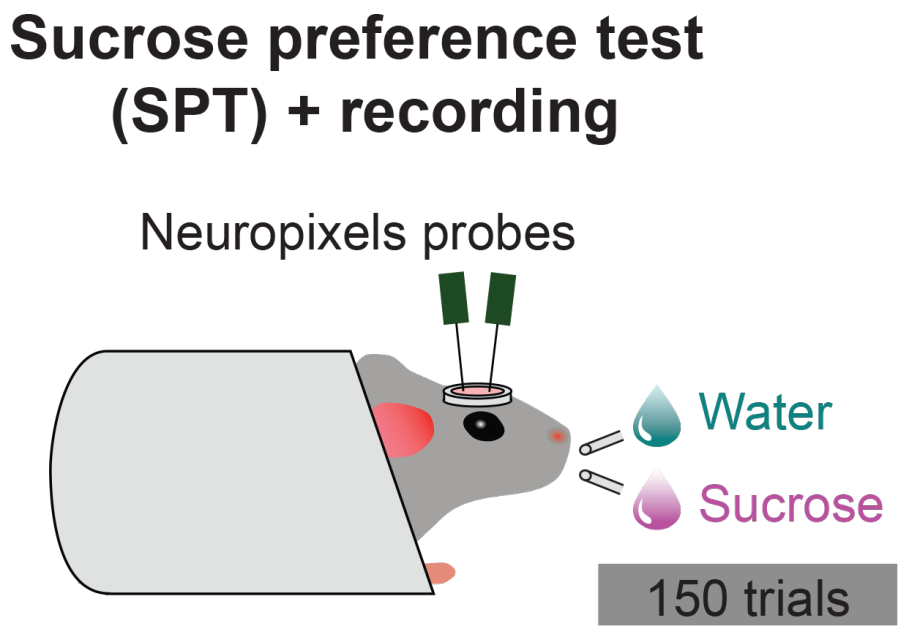
Susceptible mice have a greater number of distinct states in the BLA at rest

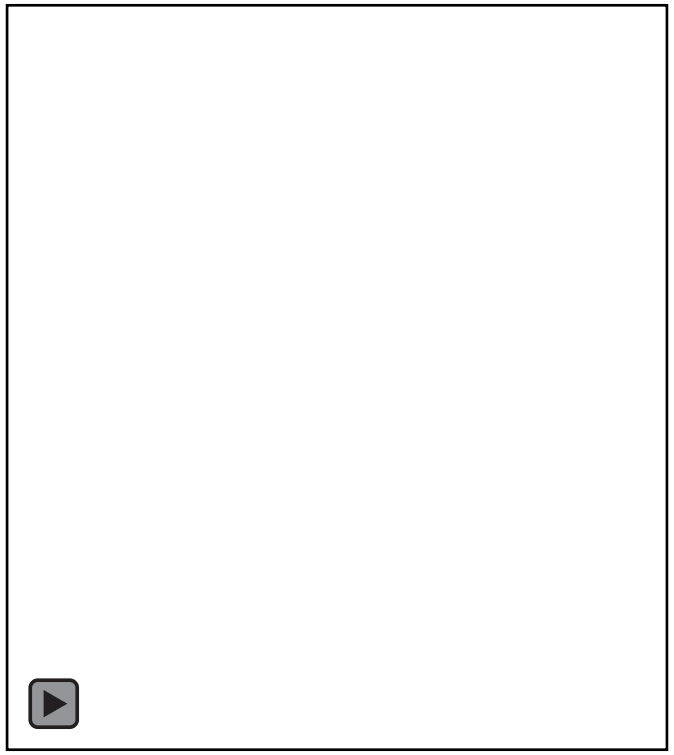






Do these extra population states in the amygdala disrupt normal reward processing in susceptible mice?





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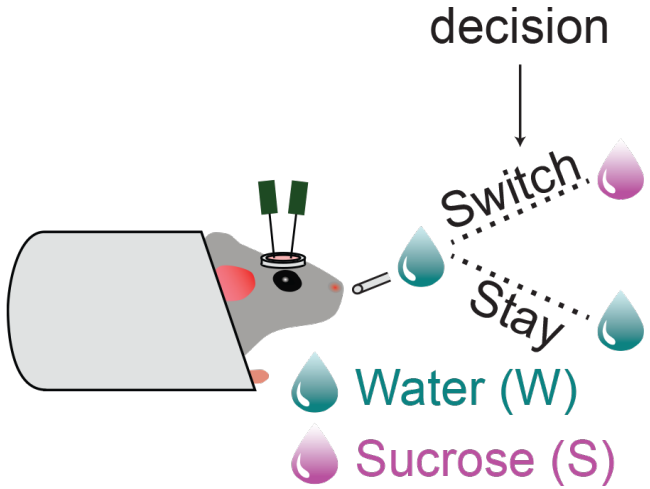
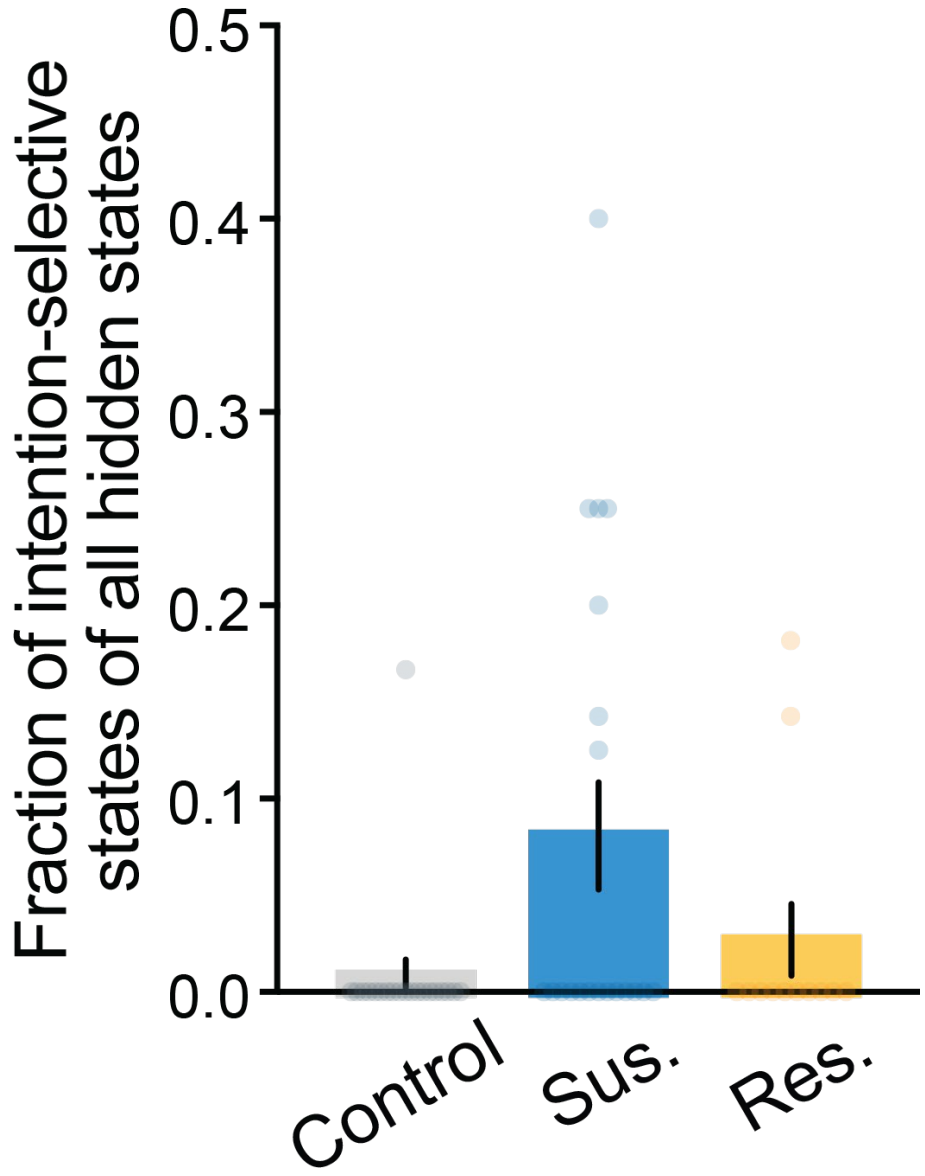
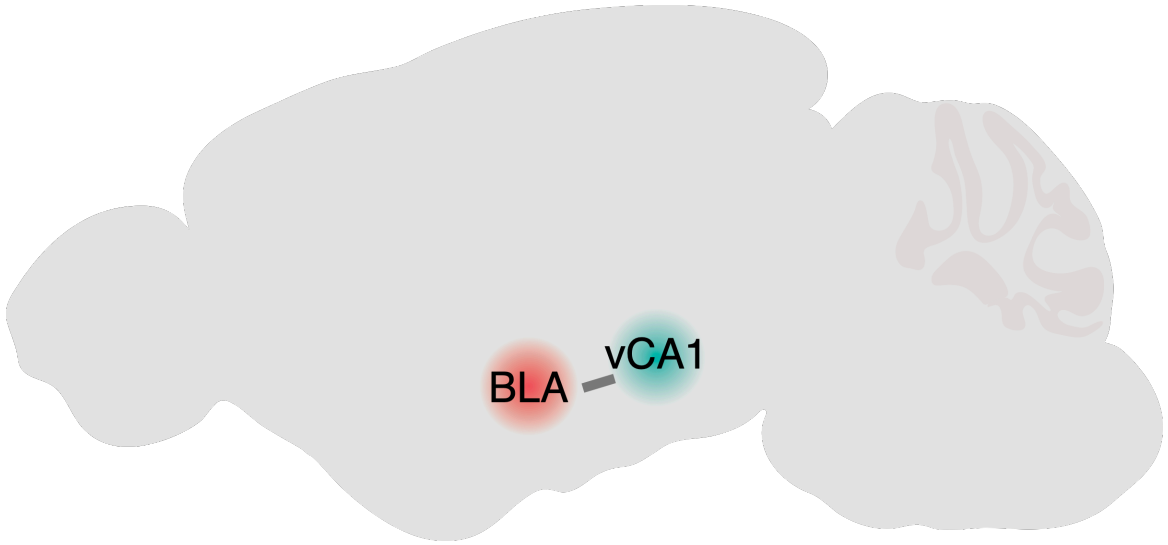
Intrusive, rumination-like, neural states during decision making in the BLA of susceptible mice





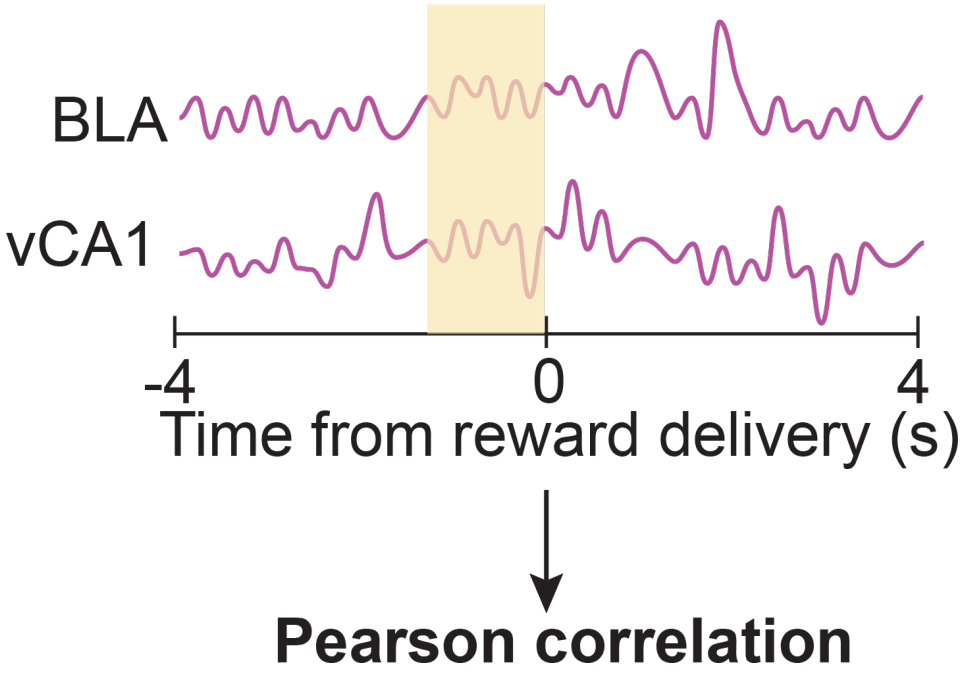


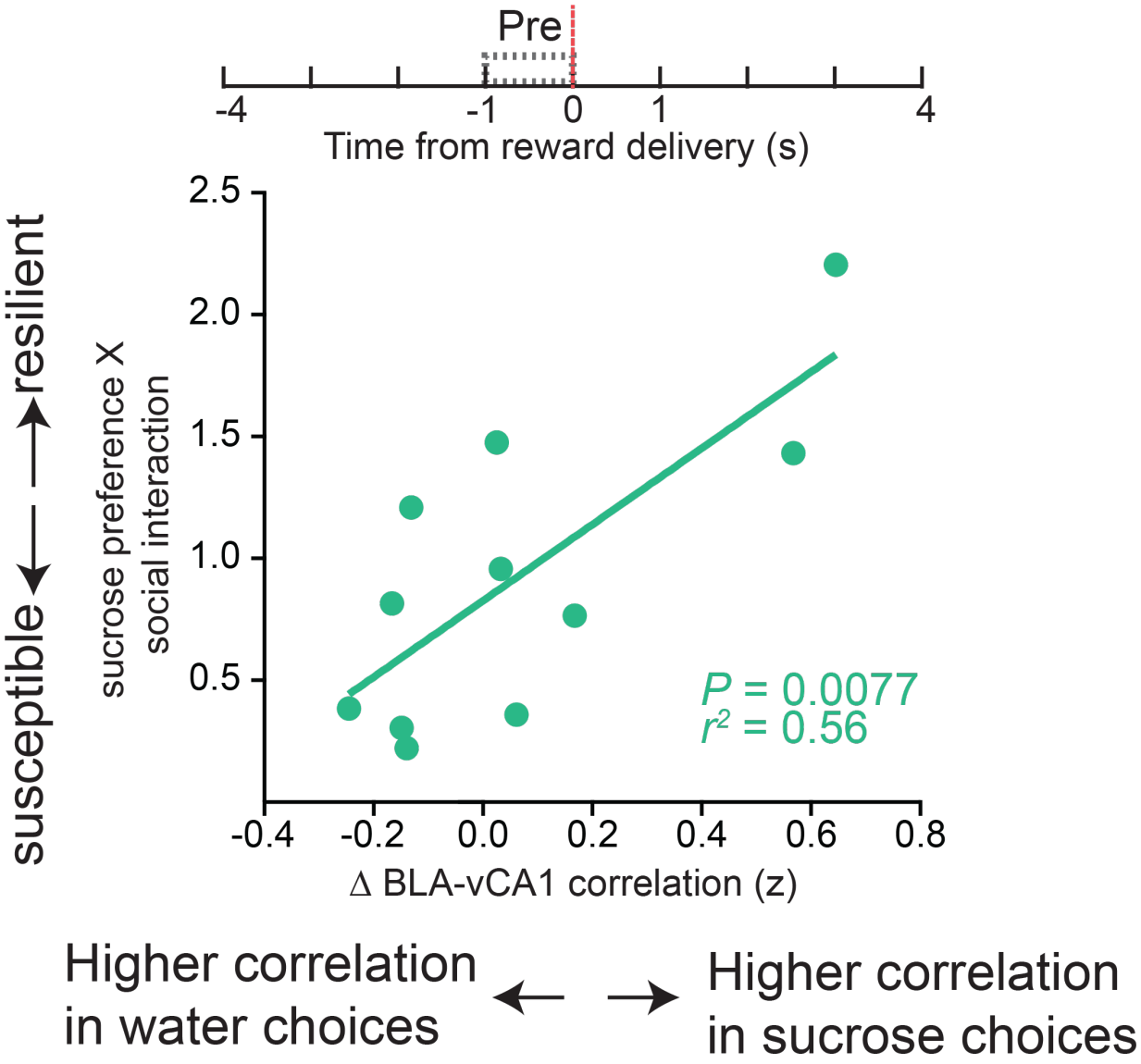
Ventral hippocampus (vCA1) provides dense input to the amygdala.

vCA1 and BLA represent **reward identities** and are sensitive to **stress**.

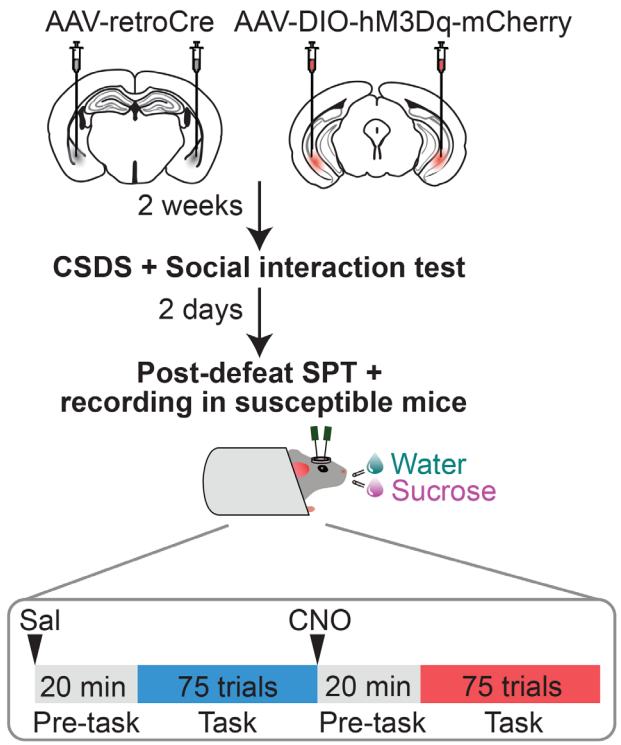
Can targeting this circuit improve stress outcomes?

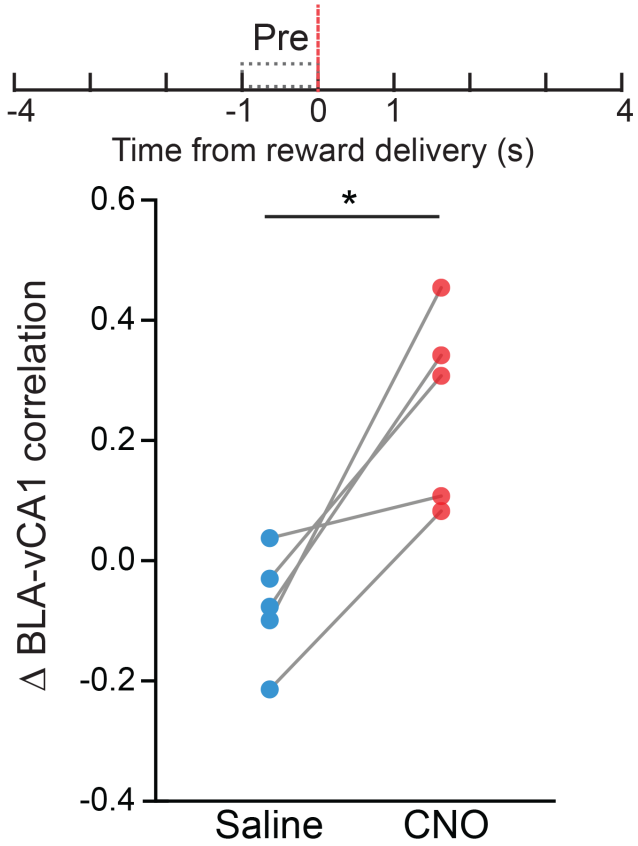
Strength of vCA1-BLA interaction is correlated with resiliency





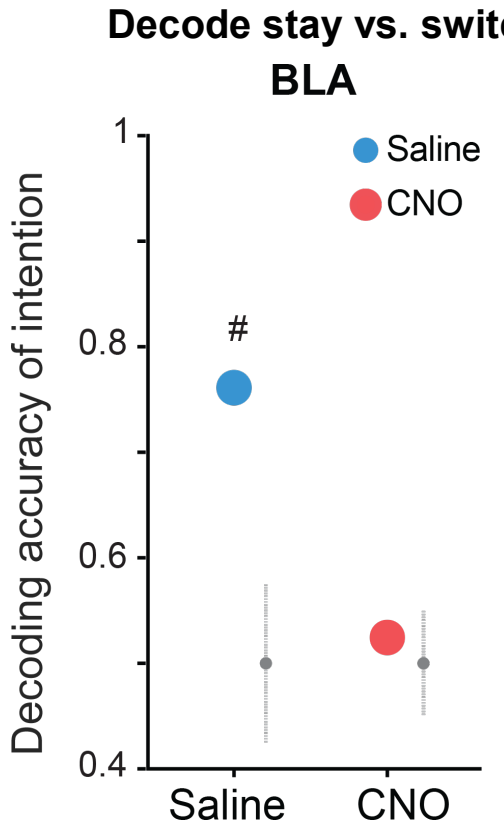
Rescue of neural activity signatures of anhedonia-like behavior by circuit-specific manipulations

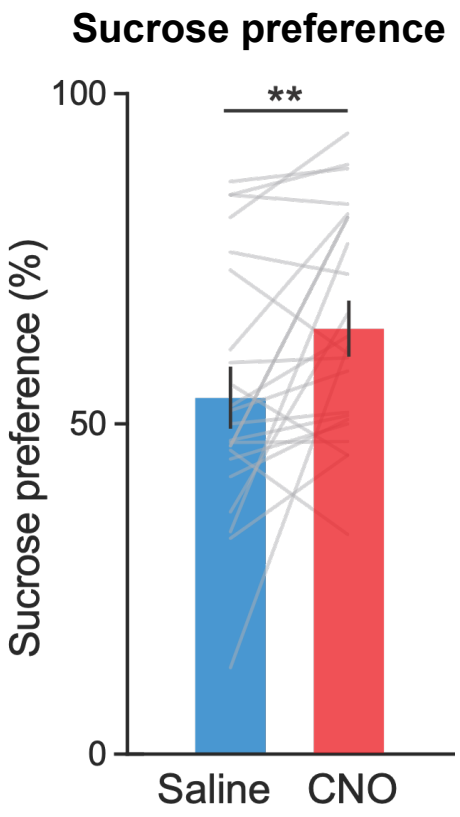




Susceptibility signature

Anhedonia-like behavior





Conclusions

Resting BLA activity distinguishes susceptible, resilient, and control mice.

Intrusive, rumination-like, BLA population states in susceptible mice disrupt reward processing.

vCA1-BLA manipulation restores neural dynamics and rescues anhedonia.

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