An Examination of Basolateral Amygdala (BLA) Astrocyte Calcium-Signaling Dynamics Involved in Fear-Memory Recall

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Introduction

- **Astrocytes** are a subtype of glial cells that make up the majority of cells in the human central nervous system (CNS).
  - They perform key metabolic, homeostatic functions, and serve as cellular regulators within the brain.

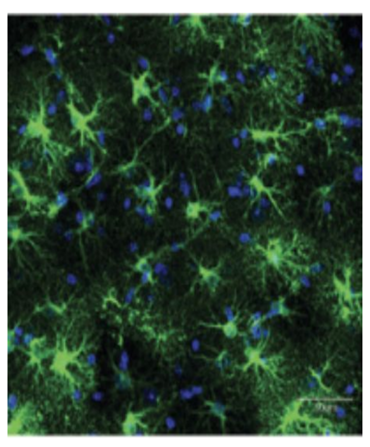


Figure 1. (Ryan Senne et al., 2023)

- The **basolateral amygdala (BLA)** is involved in fear memory processing in the brain, as well as cognition, stress responses, and motivation.
- It is currently unclear how memory recall and extinction sessions differ, and it is possible that the difference in these sessions could be represented in the unique signaling of both neurons and glial cells.
- **Goal:** To examine how BLA astrocytes are involved in fear memory recall and determine if we can extract differences in the **underlying calcium dynamics** across a fear recall session using fiber photometry data of BLA astrocytes in mice.

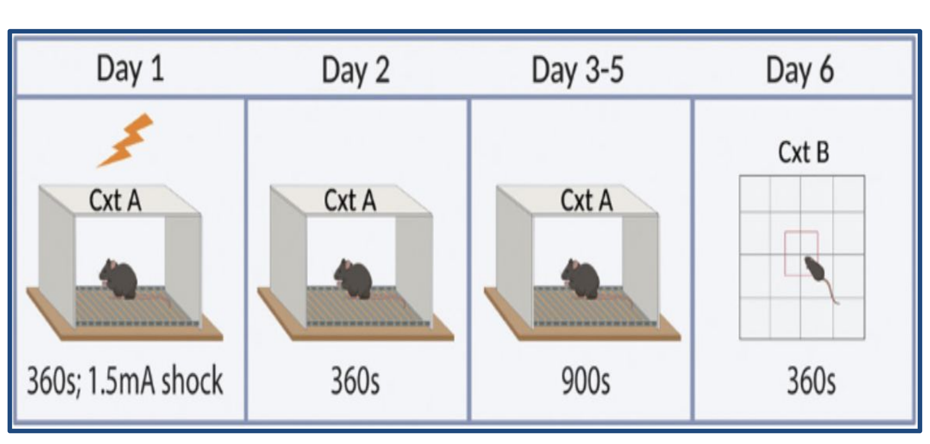


Figure 2. Behavioral paradigm. (Ryan Senne et al., 2023), illustrates mice receiving shocking treatment over a period of time, the condition of recall of fear memory.

Results

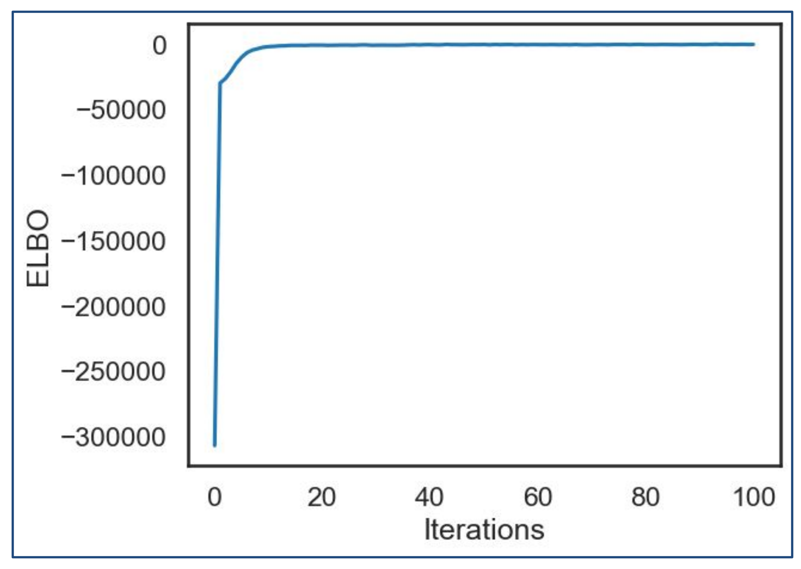
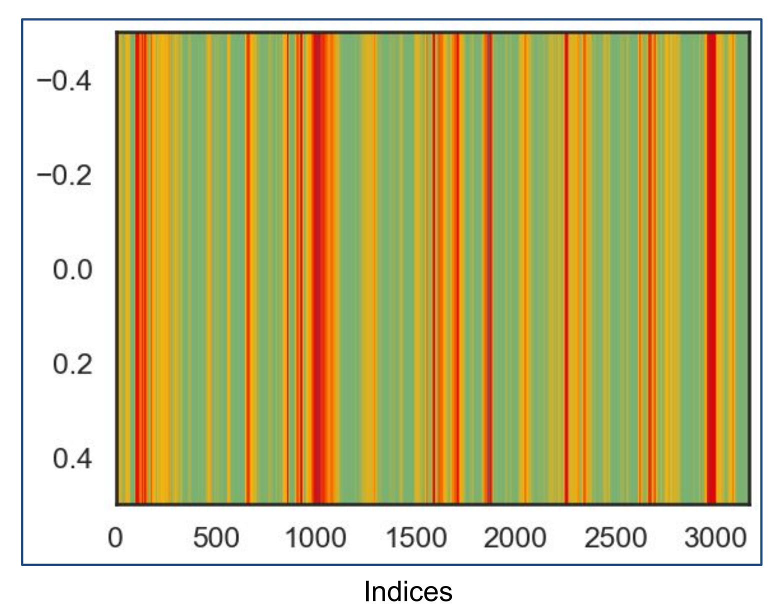


Fig 5. Grid search over the number of latent states for the continuous and discrete states in order to maximize model performance. The ELBO graph represents the fit of the finalized model and converges at a higher dimension.

Fig 6. Predicted discrete hidden states at each recorded measurement of time. No meaningful task structure reflected.

- State 3
- State 2
- State 1



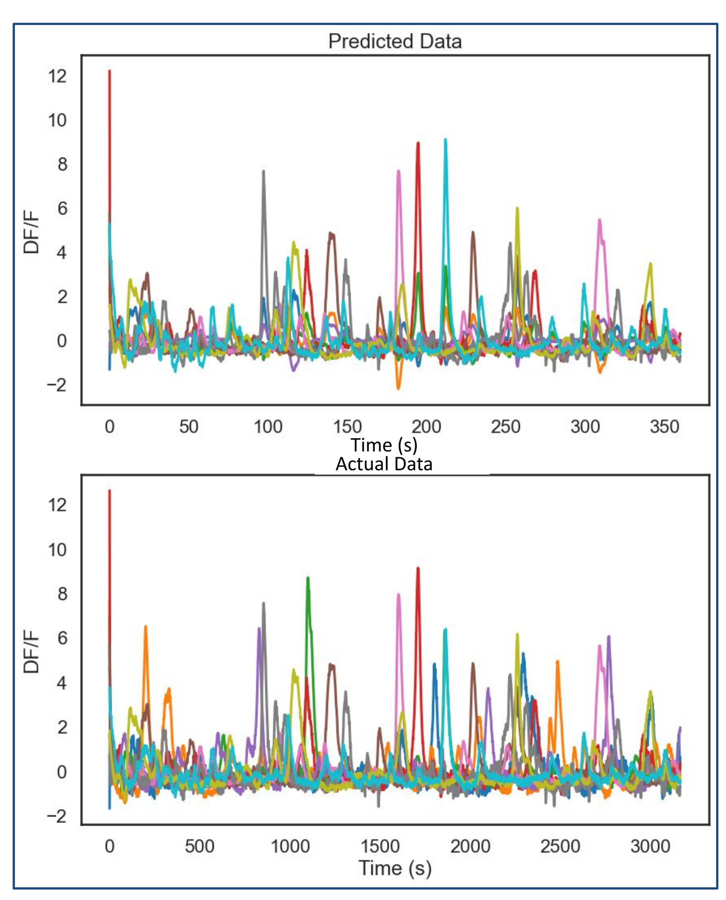
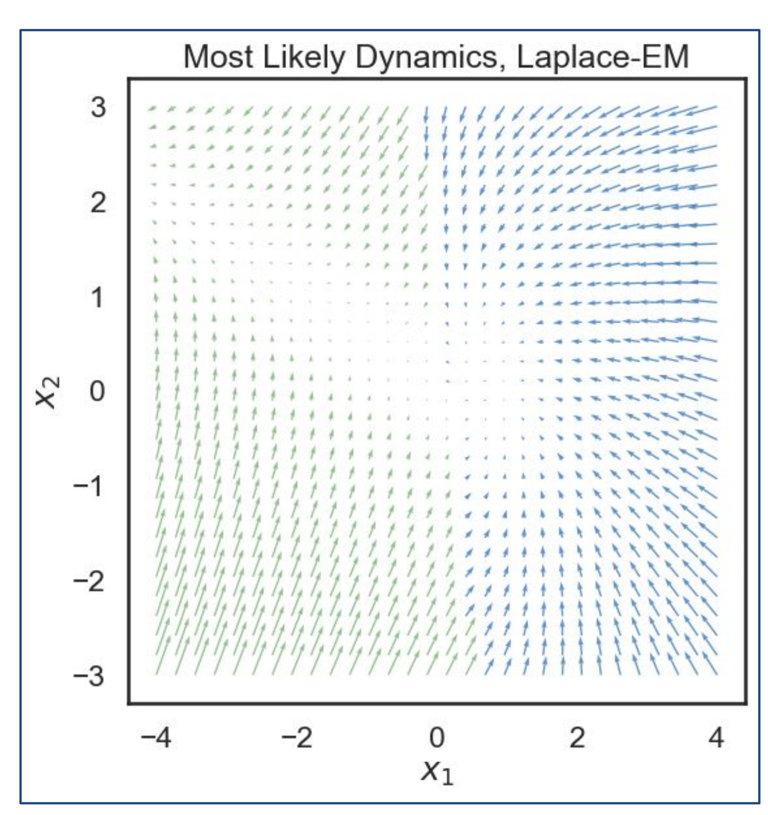


Fig 7. Predicted Measure of Fluorescence of Calcium Signaling over time from the model (top) vs. true data (bottom). Shows the deviations from the true data.

Fig 8. Phase Plane of the first two continuous hidden states. An approximate line attractor and sink node are present in the data.



Discussion

- The hidden continuous states are modeled as gaussian orthogonal emissions, which resembles principal component analysis (PCA) modes.
- The discrete states represent changes in the data generating process that could be akin to brain states changing.
- The model is sufficient for finding the most likely hidden states given BLA astrocyte fiber photometry data, however, it is unclear whether these states are meaningful as they did not have obvious analogues to behavioral data or task structure.
- Based on the calcium fluorescence data obtained from Fig 7, we can see there is there is some variance between the actual data and predicted data, indicating a model somewhat misspecified to correlate calcium signaling and the hidden states.
- Phase plane analysis of the first two continuous hidden states reveals both an apparent line attractor and a sink node. The sink is likely the baseline of the photometry recording. Future work could look at deciphering the line attractor topology.

Limitations

- We cannot assess variance within the amygdala of individual animals because the model is focused on analyzing the fiber photometry data between different animals. Rather, this model shows us if there is something shared within the states that causes changes in the brain.

Future Work

- Our model is not as low dimensional as we hoped, but we can build a more efficient model by adding a regression framework as well as building in freezing behavior in the model. This would help better represent the calcium signaling as a function of hidden states and better interpret our data.
- Discovering the involvement of astrocyte calcium signaling in fear-memory recall can help refine our understanding of memory processing, especially in the context of fearful states.
- Analyzing an individual's astrocyte calcium dynamics, through techniques such as calcium imaging, might give us a greater understanding of psychiatric disorders, and can potentially lead to more personalized treatment strategies to optimize fear memory modulation based on the specific needs of the patient.

Methods

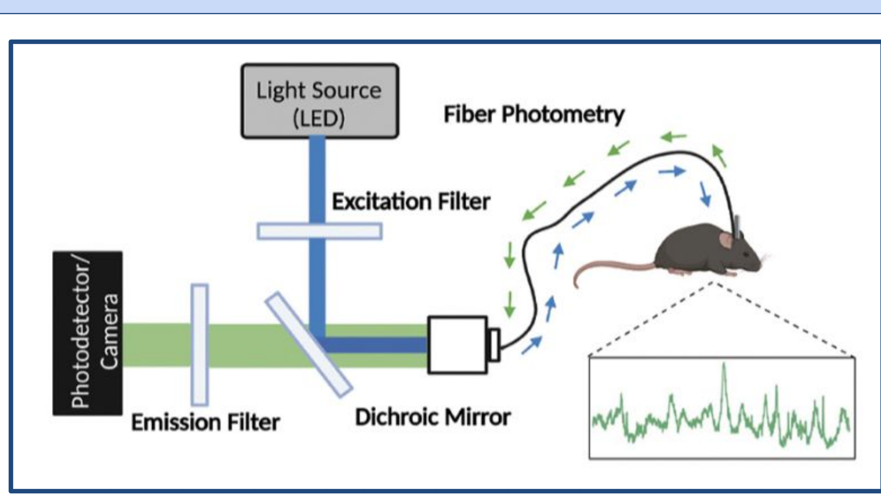


Figure 3 In vivo fiber photometry setup. (Ryan Senne et al., 2023)

- The study used a **fiber photometry** setup to observe the activity of astrocytes in freely moving mice.
  - A specific **wavelength** of light was delivered to the astrocytes using a patch cord and fiber optic implant.
  - The emitted signal from the **astrocytes** was collected and processed using various filters and a scientific camera.
  - Simultaneously, a separate signal was recorded to account for other factors like motion and autofluorescence in the tissue.

- We modeled the normalized fluorescent calcium signals (DF/F) recorded from BLA astrocytes using a **recurrent switching linear dynamical system (rSLDS)**. This method linearizes a possible highly non-linear system by finding a set of potentially meaningful modes that can be described with linear dynamics.
- To optimize this model, we performed a **grid search** across the discrete state dimension, K, and the dimension of the continuous hidden state, D. For model selection we found the best combination of the parameters that maximize the **evidence lower bound (ELBO) measurement**. This procedure is equivalent to a **5-fold cross validation regime.**

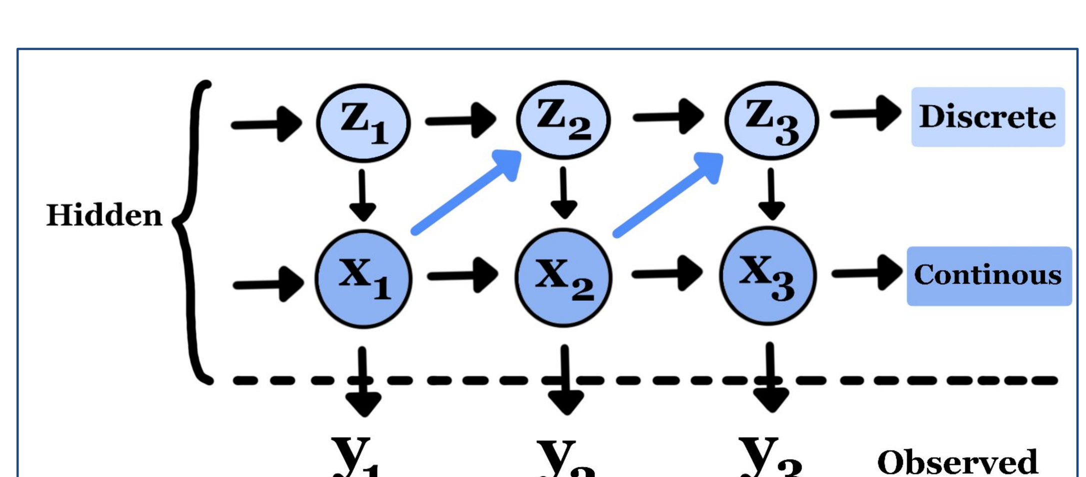


Figure 4. Recurrent Switching Linear Dynamical System. (Irene Jiang)

References

1. Suthard RL, Senne RA, Buzharsky MD, Pyo AY, Dorst KE, Diep AH, Cole RH, Ramirez S. Basolateral Amygdala Astrocytes Are Engaged by the Acquisition and Expression of a Contextual Fear Memory. J Neurosci. 2023 Jul 5;43(27):4997-5013. doi: 10.1523/JNEUROSCI.1775-22.2023. Epub 2023 Jun 2. PMID: 37268419; PMCID: PMC10324998.
2. Aditya Nair, Tomomi Karigo, Bin Yang, Surya Ganguli, Mark J. Schnitzer, Scott W. Linderman, David J. Anderson, Ann Kennedy. An approximate line attractor in the hypothalamus encodes an aggressive state. Volume 186, Issue 1, 2023, Pages 178-193.e15, ISSN 0092-8674, https://doi.org/10.1016/j.cell.2022.11.027.

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