Engrams: Memory Retrieval and Forgetting

Sowmya Manojna Narasimha

1 December 2022

Introduction

Memory

- Encoding, consolidation, retrieval and storage.
- Engrams are physical substrates of memory.
- Neurons that are activated by learning and memory retrieval could form the cellular substrate of engrams.

Aim

- Can we identify these engram neurons?
- How do they differ from the non-engram neurons?
- What are the molecular changes that cause these differences?

Aim

- Can we identify these engram neurons?
- How do they differ from the non-engram neurons?
- What are the molecular changes that cause these differences?

Aim

- Can we identify these engram neurons?
- How do they differ from the non-engram neurons?
- What are the molecular changes that cause these differences?

Engrams

Engram Identification

- Conditional gene expression and activity based gene expression.
- Localized learning
- Overlap between learning and memory retrieval neurons.
- Correlation doesn't imply causation.

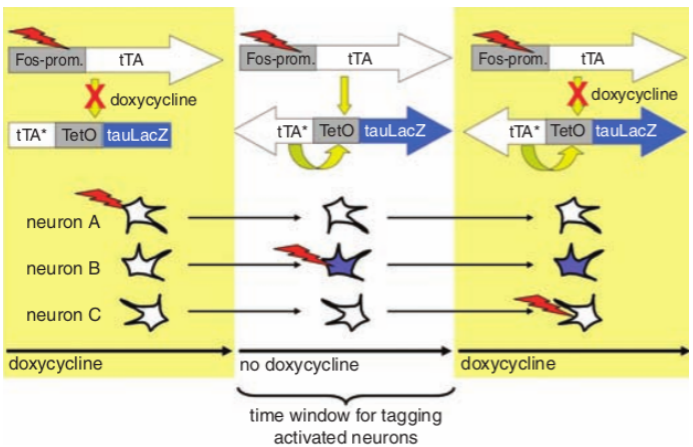

Figure 1: TetTag system used for engram identification. [1]

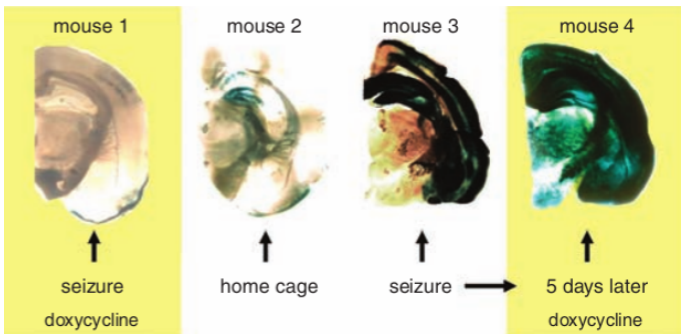

Figure 2: TetTag system causes all the active neurons during DOX-off condition to be tagged. [1]

Is Engram activation necessary and sufficient for memory retrieval?

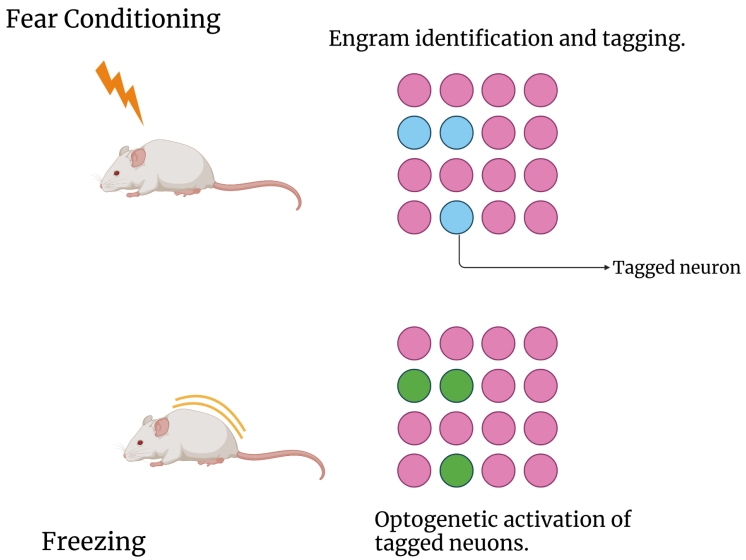

Figure 3: Engram cell activation is sufficient for memory retrieval [2].

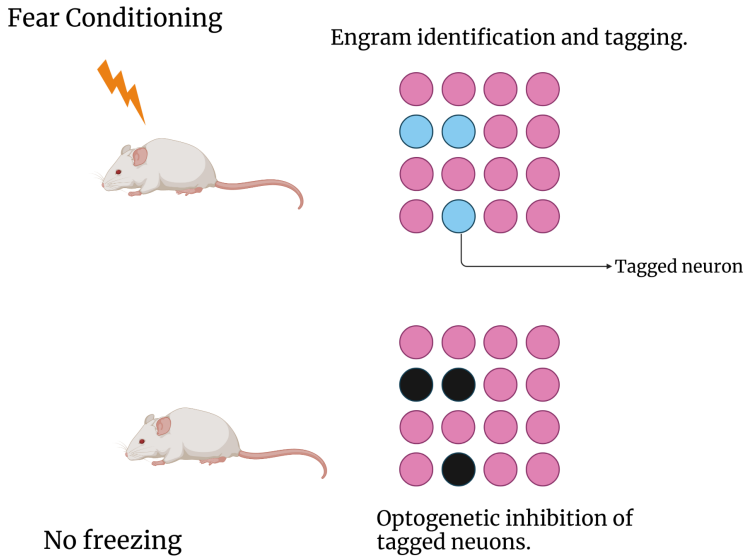

Figure 4: Engram cell activation is necessary for memory retrieval [3].

- *c-fos*-tTA mice
- AAV-TRE-ChR2-EYFP vector; ChR2 enables optogenetic stimulation.
- Engram activation is sufficient for memory retrieval.

- *c-fos*-tTA/tetO-Cre/tetO-H2B-GFP mice
- AAV-FLEX-Archaerhodopsin (ArchT) vector; ArchT enables optogenetic inhibition.
- Engram activation is necessary for memory retrieval.

How do engram cells differ from non-engram cells?

How do engrams differ from non-engram cells?

- EPSC amplitude is higher in engram cells than non-engram cells.
- AMPAR/NMDAR current ratio is higher in engram cells.
- Engram cells have higher dendritic spine density.
- If these characteristic are reversed, is memory retrieval disrupted?

Memory Retrieval

Does reversal of the physiological changes affect memory retrieval?

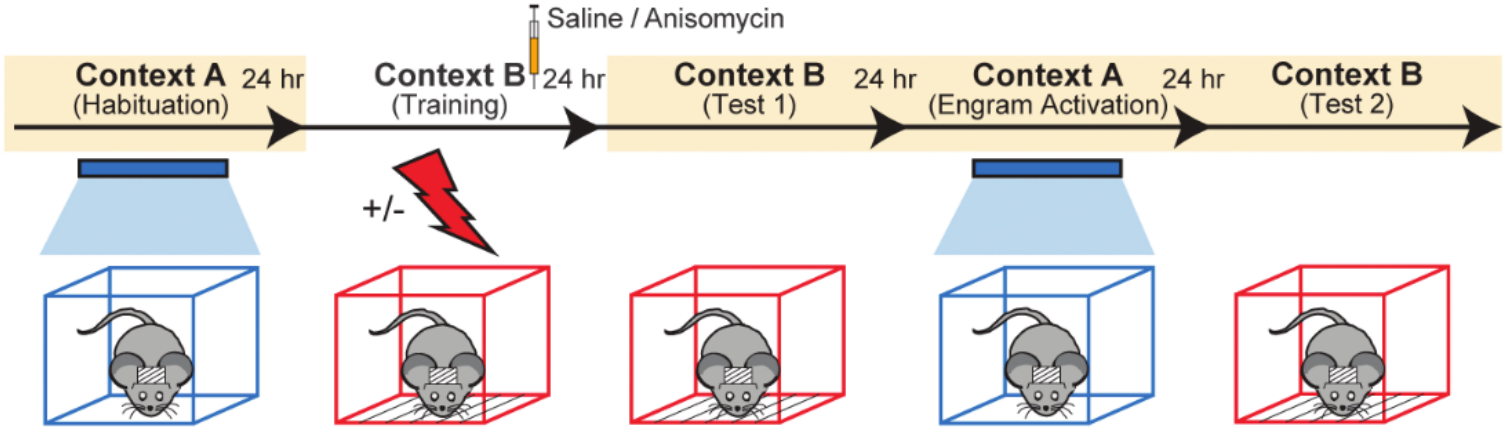

Figure 5: Amnesia induction and reversal of physiological changes [4].

- Protein synthesis inhibition reversed all physiological changes.
- Optogenetic activation rescued memory retrieval
- Memory storage is still intact in induced retrograde amnesia. Only the retrieval is impaired.
- Memory consolidation is protein synthesis dependent.
- Is memory retrieval protein synthesis dependent?
- Protein synthesis inhibitors applied just prior to memory retrieval resulted in forgetting.

LTP AND LTD MEDIATED MEMORY RETRIEVAL

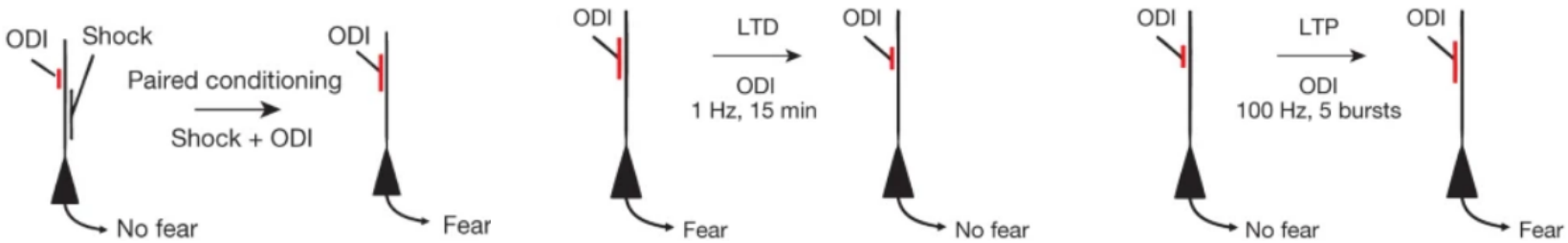

Figure 6: Experimental set up used to provide a causal link between LTP/LTD and memory retrieval [5].

- Upon inducing LTD, memory retrieval is impaired.
- Upon inducing LTP, memory retrieval is rescued.
- This process is highly plastic and can be repeated multiple times.
- LTP is both necessary and sufficient for memory retrieval.
- What is the role of AMPAR, NMDAR in memory retrieval?

Molecular Basis

Role of AMPAR and NMDAR in memory retrieval.

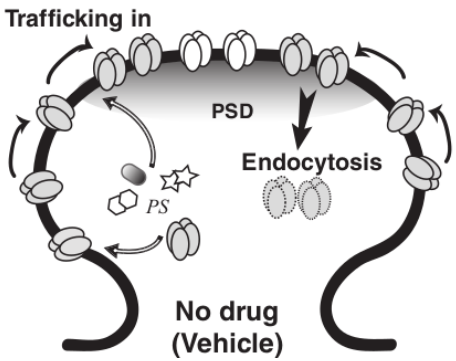

Figure 7: Process of AMPAR trafficking at the synapse. The image depicts both NMDAR mediated and non-NMDAR mediated AMPAR trafficking.

- NMDAR inhibitors
  - Prevent AMPAR recycling
  - Maintain constant density of AMPAR at the synapse
  - Prevent decay of short term memory.
- $GluA2_{3Y}$ prevents endocytosis of AMPAR and hence, prevents decay of short term memory.
- PKMζ prevents endocytosis of AMPAR and doesn't result in hindered memory retrieval.
- $GluA2_{3Y}$ mediated prevention of AMPAR endocytosis significantly decreased memory loss in Alzheimer's animal models.

Conclusions

Conclusion

The review covered topics related to

- Engram identification, activation and their role in memory retrieval.
- The effects of the physiological changes of engrams in their ability to retrieve memories.
- The molecular basis underlying the engram's ability to retrieve information.
- Engram accessibility mediated forgetting.

Future Directions

- What happens during memory storage? What are the mechanisms mediating it?
- Do multiple engrams interact? If so, how do they interact at the network level?
- The biological basis of memory storage can be incorporated into reinforcement learning agents, creating efficient continual learning, while avoiding catastrophic forgetting.

Reference

References I

- L. G. Reijmers, B. L. Perkins, N. Matsuo, and M. Mayford, "Localization of a stable neural correlate of associative memory," *Science*, vol. 317, no. 5842, pp. 1230–1233, 2007.
- X. Liu, S. Ramirez, P. T. Pang, C. B. Puryear, A. Govindarajan, K. Deisseroth, and S. Tonegawa, "Optogenetic stimulation of a hippocampal engram activates fear memory recall," *Nature*, vol. 484, no. 7394, pp. 381–385, 2012.
- K. Z. Tanaka, A. Pevzner, A. B. Hamidi, Y. Nakazawa, J. Graham, and B. J. Wiltgen, "Cortical representations are reinstated by the hippocampus during memory retrieval," *Neuron*, vol. 84, no. 2, pp. 347–354, 2014.
- T. J. Ryan, D. S. Roy, M. Pignatelli, A. Arons, and S. Tonegawa, "Engram cells retain memory under retrograde amnesia," *Science*, vol. 348, no. 6238, pp. 1007–1013, 2015.
- S. Nabavi, R. Fox, C. D. Proulx, J. Y. Lin, R. Y. Tsien, and R. Malinow, "Engineering a memory with ltd and ltp," *Nature*, vol. 511, no. 7509, pp. 348–352, 2014.