Synapse-specific plasticity governs the identity of overlapping memory engrams

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Abstract

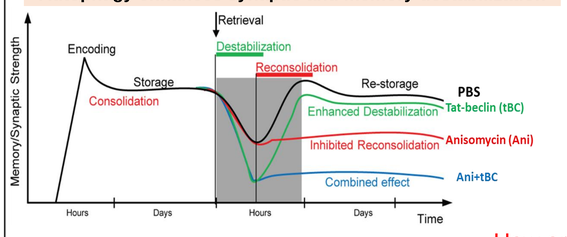
Throughout the life, we form several memories that are encoded in specific neuronal ensemble, called engram cells. Some of these memories are associated and stored in shared ensemble. However, brain machinery that underlies memory storage and defines certain memory identity amidst numerous number of memories stored in the same ensemble is poorly understood.

Here we show that when two associative memories are encoded in shared ensemble, engram-specific synaptic plasticity delineates specific memory entity and that specific plasticity is both sufficient and crucial for information storage. Using auditory fear conditioning and c-fos-TetTag system, optogenetic stimulation of the activated ensemble terminals of auditory cortex (AC) and medial geniculate nucleus (MGm) in lateral amygdala (LA) after complete retrograde amnesia -accomplished by autophagy induction with protein synthesis inhibition- failed to induce memory recall at recent and remote time points, indicating that memory engram no longer exists in that circuit. This result was correlated with the resetting of plasticity and functional connectivity between the engram assemblies. Furthermore, potentiating or depotentiating the plasticity at synapses specific to a given memory did not affect the linked memory that is encoded in the same ensemble, suggesting that memories are stored in specific synapses.

These findings unravel how the brain organizes and stores multiple associative memories in shared ensemble, underpinning a causal relationship between synaptic input-specific plasticity and memory identity and storage. Moreover, our study sheds light on the capability of selective and integral erasure of memory trace from the engram network, suggesting a potential way to treat post-traumatic stress disorder (PTSD).

Introduction

Autophagy enhances synaptic and memory destabilization



Associated memories are stored in shared ensembles

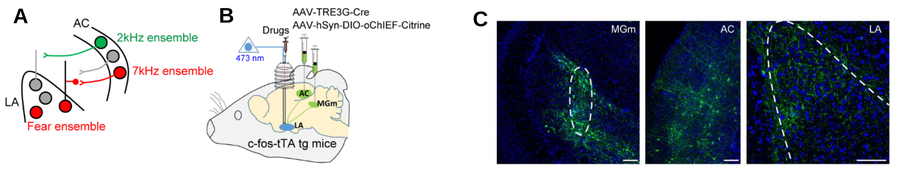
Aim of the work

What is the fundamental substrate for memory storage ?

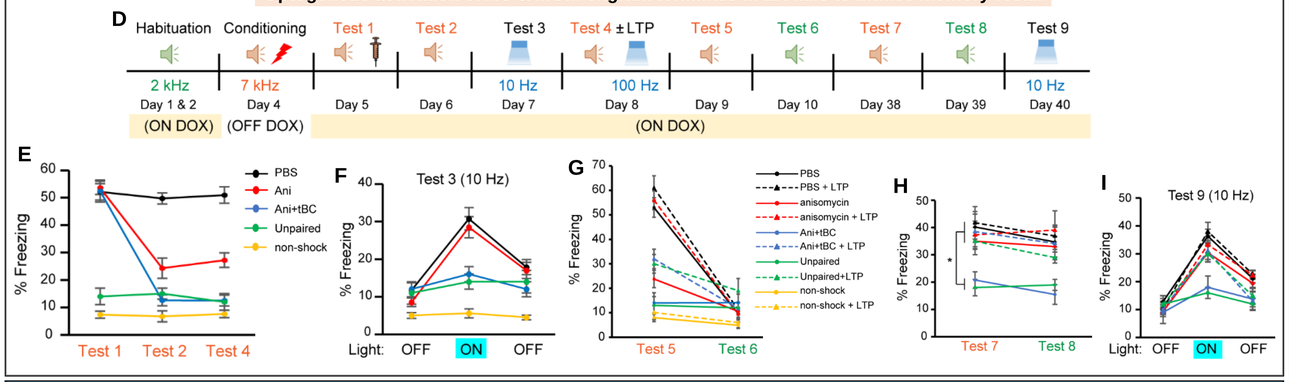
How are multiple associated memories identified in the shared ensemble ?

① Engram circuit loses the memory after complete amnesia

Sparse labelling of AC & MGm engram cells

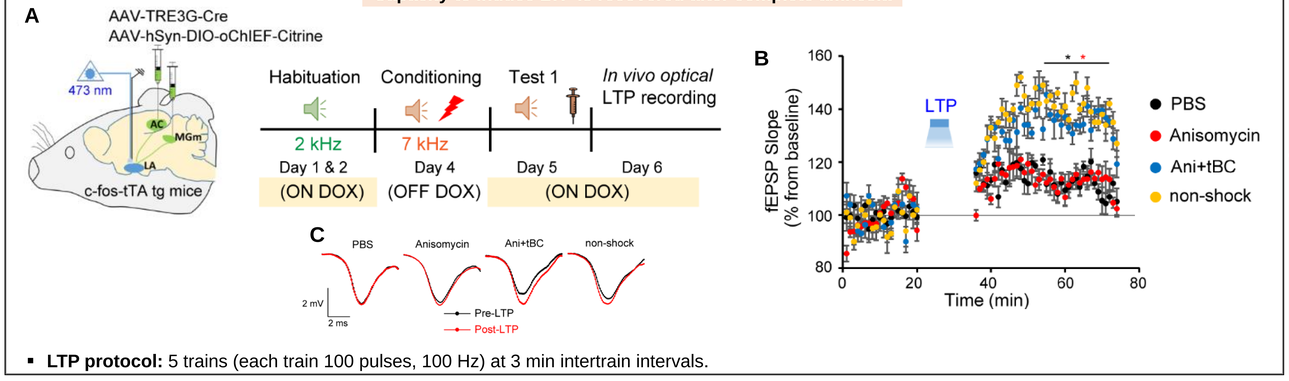


Optogenetic activation of AC & MGm engram terminals in LA fails to induce memory recall



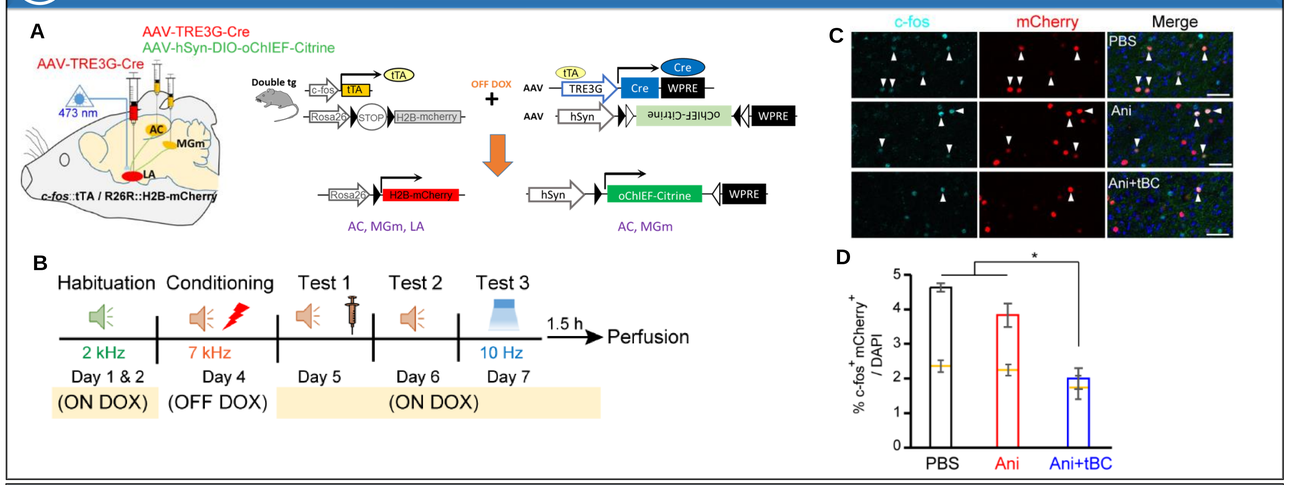
② Resetting of synaptic plasticity after complete retrograde amnesia

Capacity to induce LTP is recovered after complete amnesia

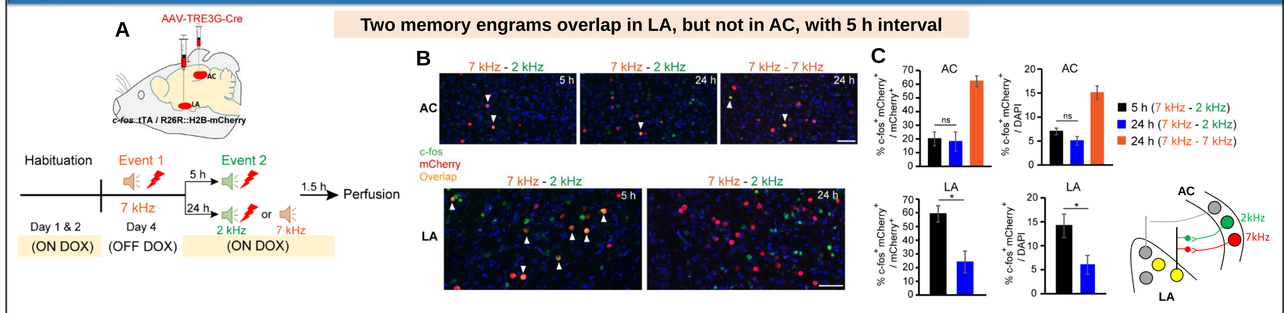


- **LTP protocol:** 5 trains (each train 100 pulses, 100 Hz) at 3 min intertrain intervals.

③ Functional connectivity between engram cells is disrupted after complete amnesia



④ Synapse-specific plasticity within engram circuit denotes memory trace identity



Conclusion

- Engram network no longer stores the memory after complete retrograde amnesia.
- Resetting of synaptic plasticity and functional connectivity between engram assemblies as neural correlates of complete amnesia.
- Memories, stored in engram cells, are synapse specific.
- Synapse-specific plasticity guarantees the storage of specific fear memory identity.