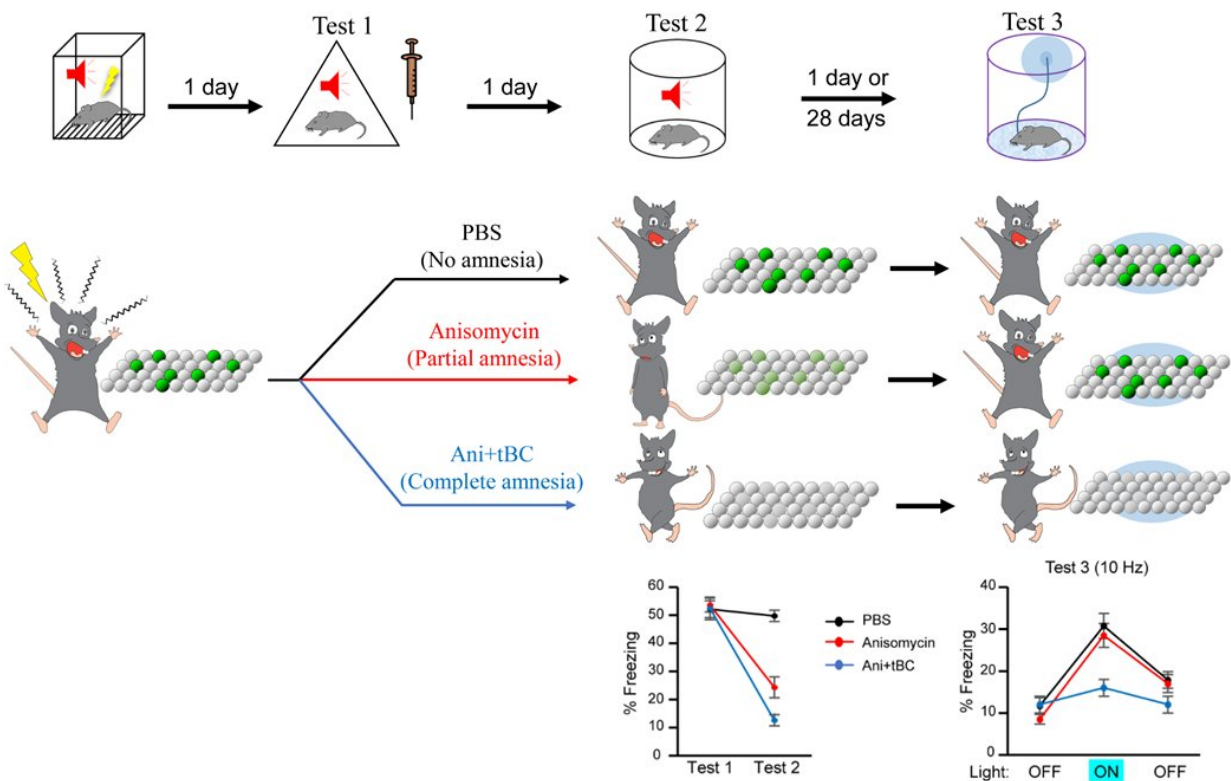


Synapse-specific plasticity governs the identity of overlapping memory traces

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Mice were exposed to auditory (7 kHz) fear conditioning. They received injection of phosphate buffered saline (PBS) or anisomycin or anisomycin+tat-beclin (Ani+tBC), after recalling the memory (test 1). PBS-treated mice showed higher freezing response while anisomycin-treated mice showed partial decrease in the freezing response (partial retrograde amnesia), whereas Ani+tBC induced complete retrograde amnesia (test 2). Optogenetic activation of the neurons, storing the 7kHz fear memory, induced freezing in the PBS and anisomycin

groups, while the Ani+tBC group continued to show complete retrograde amnesia (test 3). Credit: Kaoru Inokuchi, Kareem Abdou

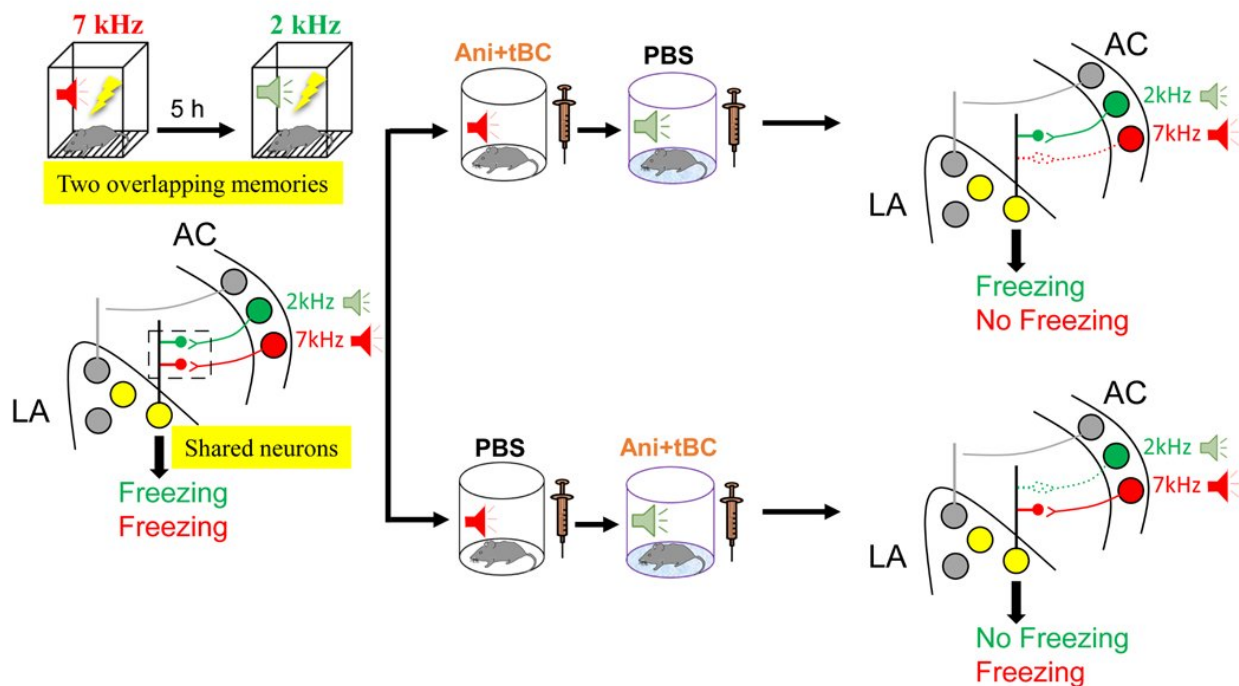
Memories are formed through long-term changes in synaptic efficacy, a process known as synaptic plasticity, and are stored in the brain in specific neuronal ensembles called engram cells, which are activated during corresponding events. When two memories are associated, cell ensembles corresponding to each memory overlap. However, each memory has its own identity. How the brain stores and defines a specific memory identity when two memories interact and are encoded in the shared ensemble was elusive. Now, a research team led by Dr. Kaoru Inokuchi at the University of Toyama shows that synapse-specific plasticity represents specific memory entities, and that synaptic plasticity between specific engram assemblies is both sufficient and crucial for information storage.

They exposed mice to auditory fear conditioning in which a tone was associated with a foot shock. Synaptic plasticity between the auditory cortex (AC) and the medial part of medial geniculate nucleus (MGm) neuron terminals and the lateral amygdala (LA) neurons mediates this association. After complete retrograde amnesia, optogenetic stimulation of the activated ensemble terminals of the AC and the MGm in the LA failed to induce [fear memory](#) recall (Figure 1), indicating that the memory engram no longer existed in that circuit. This result was correlated with the resetting of synaptic strength and functional connectivity between engram assemblies.

Next, mice were fear conditioned to two different tones, separated by five hours. Therefore, the two memory traces interacted and overlapped in LA. Complete retrograde amnesia of a given fear memory did not affect the linked fear memory encoded in the shared ensemble (Figure

2), indicating that memories are stored in specific synapses.

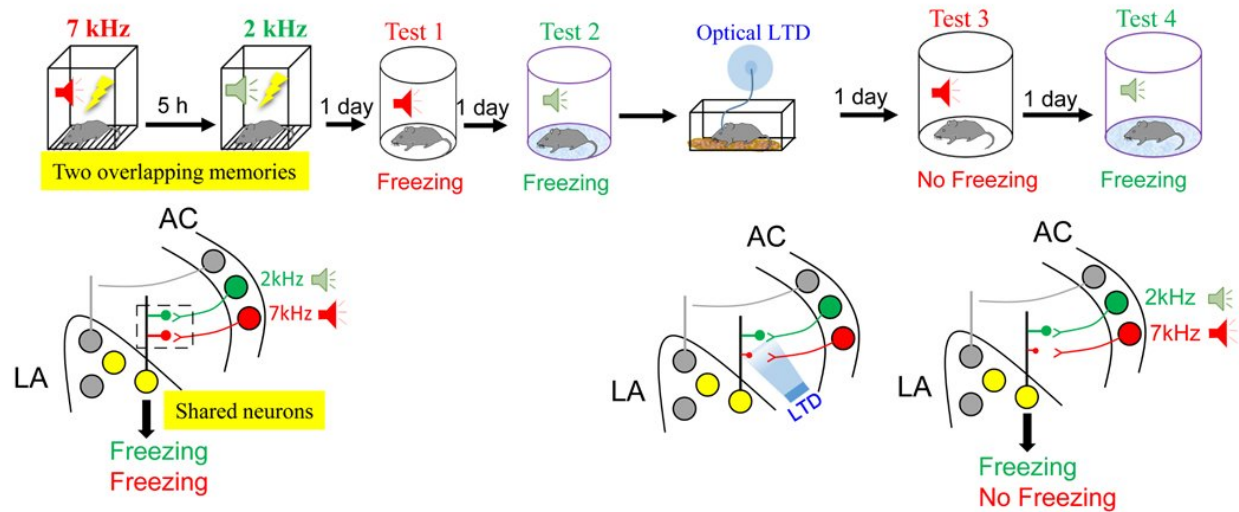
Then, the researchers addressed the question of how each memory reserves its individual identity within the shared ensemble. They used optical long-term depression (LTD) to depotentiate the synaptic efficacy in synapses specific for certain memory. Depotentiation of the plasticity at synapses specific to one memory deconstructed the specific connectivity between engram assemblies, thereby affected the recall of only that memory without influencing the linked memory in the same population of neurons (Figure 3). Thus, sharing of engram cells underlies the linkage between memories, while synapse-specific plasticity guarantees the identity and storage of individual memories.



Mice were exposed to two auditory fear conditioning, separated by five hours.

Both memories were encoded by shared neurons in the lateral amygdala (LA) while they were encoded by different neurons in the auditory cortex (AC). Injecting combination of anisomycin+tat-beclin after retrieving certain memory, erased that specific memory without affecting the other linked memory that was stored in the shared neuronal ensemble. Credit: Kaoru Inokuchi, Kareem Abdou

The findings demonstrate that synapse-specific plasticity is necessary and sufficient for associative fear memory storage, and it guarantees uniqueness to the memory trace, advocating the plasticity as a substrate for the fear memory engram. Furthermore, they achieved selective and total erasure of [fear](#) memory from an engram network without affecting other memories stored in the shared ensemble by resetting the plasticity in a synapse-specific manner. This leads to better understanding of the mechanisms underlying [memory](#) storage, and may give insight into therapeutic ways to treat post-traumatic stress disorder.



Mice were exposed to two auditory fear conditioning, separated by five hours. Both memories were encoded by shared neurons in the lateral amygdala while they were encoded by different neurons in the auditory cortex. Mice showed freezing behavior in response to 7kHz and 2kHz tones. Induction of optical long term depotentiation (LTD) to synapses specific to 7kHz fear memory, erased only that memory (test 3) without affecting the other memory (test 4) that was stored in shared neuron ensemble. Credit: Kaoru Inokuchi, Kareem Abdou

More information: Kareem Abdou et al, Synapse-specific representation of the identity of overlapping memory engrams, *Science* (2018). [DOI: 10.1126/science.aat3810](https://doi.org/10.1126/science.aat3810)

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