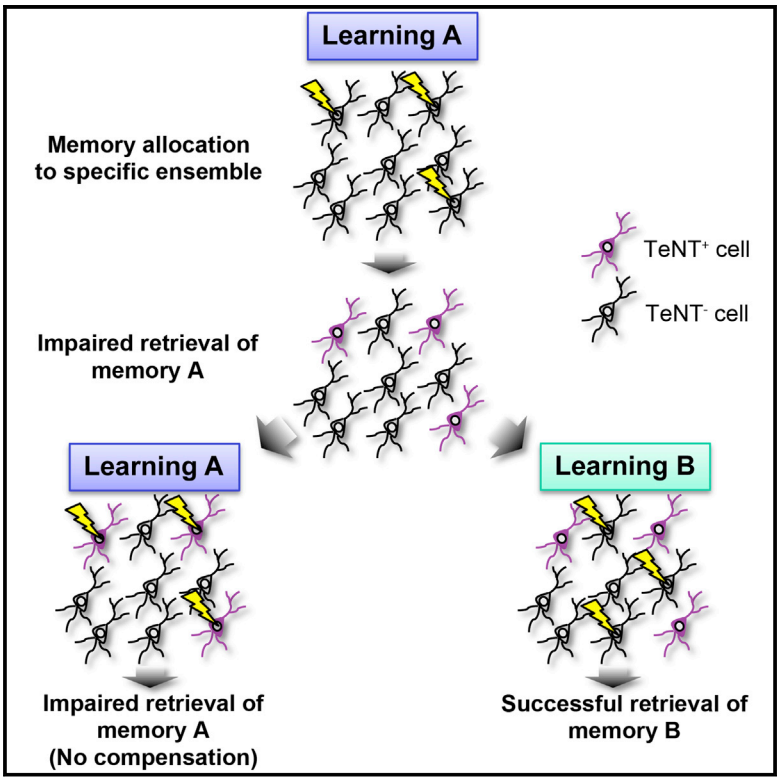
Cell Reports

Irreplaceability of Neuronal Ensembles after Memory Allocation

Graphical Abstract



Highlights

- Inhibiting learning-activated neural ensembles impairs memory retrieval
- Inhibiting neural ensembles activated during learning impairs relearning
- Inhibiting neural ensembles for a specific memory does not hinder distinct learning

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In Brief

Is the same ensemble of neurons always dedicated to the same learning? Matsuo shows that suppression of neuronal ensembles activated during initial learning hinders relearning. This ensemble inflexibility could ensure the strengthening of synaptic connections across a specific subset of neurons by repetitive activation, thereby enabling memory enhancement.

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Report

Irreplaceability of Neuronal Ensembles after Memory Allocation

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SUMMARY

Lesion studies suggest that an alternative system can compensate for damage to the primary region employed when animals acquire a memory. However, it is unclear whether functional compensation occurs at the cellular ensemble level. Here, we inhibited the activities of a specific subset of neurons activated during initial learning by utilizing a transgenic mouse that expresses tetanus toxin (TeNT) under the control of the *c-fos* promoter. Notably, suppression interfered with relearning while sparing the ability to acquire and express fear memory for a distinct context. These results suggest that the activity of the initial ensemble is preferentially dedicated to the same learning and that it is not replaceable once it is allocated. Our results provide substantial insights into the machinery underlying how the brain allocates individual memories to discrete neuronal ensembles and how it ensures that repetitive learning strengthens memory by reactivating the same neuronal ensembles.

INTRODUCTION

External information acquired through daily experiences can be internally represented and stored in the brain across several interacting regions as a memory. Recent innovative studies have begun to present direct evidence that individual memories reside in the activities of specific spatially distributed neuronal populations within neuronal networks. For instance, activity manipulation of a small, specific, dispersed subset of neurons that was activated during a learning paradigm enabled memory operations including artificial retrieval and association of a previously obtained memory in mice (Garner et al., 2012; Liu et al., 2012; Ramirez et al., 2013). These studies provided a causal sufficiency between memory engrams and the activities of specific ensembles of neurons.

The next critical question arising from this idea is how specific subsets of neurons are chosen from a large population of neurons to encode a given memory (Silva et al., 2009). Findings from recent research suggested a potential mechanism that involves neuronal competition. A subset of lateral amygdala neurons, in which cyclic AMP responsive element binding protein (CREB) was virally overexpressed, preferentially participated in auditory fear memory formation (Han et al., 2007). Moreover, the higher levels of CREB expression have been suggested to increase the intrinsic excitability of the neuron (Zhou et al., 2009). Thus, it is likely that neurons that are more excitable than their neighbors tend to be recruited for encoding a new memory (Yiu et al., 2014). However, much remains to be elucidated concerning the machinery of memory allocation. One of the most interesting questions is whether the same ensemble of neurons is always dedicated to the same learning or whether an alternate ensemble is flexibly substitutable. This question is critical, because it might explain how repeated training strengthens the memory. It has been well recognized that established memories can be strengthened by repeated rehearsal learning (Ebbinghaus, 1913). This is assumed to be based on the principle that the same neurons and synapses are engaged in the same learning, thereby enhancing the particular plasticity. However, it has not been demonstrated experimentally that such a mechanism actually exists in the brain. To address this particular question, a pinpoint approach is required to manipulate a specific neuronal population that is sparsely distributed in the tissue while leaving their intermingled neighbors intact. However, classical lesion or pharmacological approaches are not technically feasible.

To circumvent this difficulty, we used the *c-fos*-promoter-driven tTA (tetracycline-controlled transactivator) transgenic (Tg) system in mice to manipulate specific subsets of neurons in which the promoter of the *c-fos* gene, an immediate early gene, was activated during a given time window (Matsuo et al., 2008; Reijmers et al., 2007). In the present study, we set out to examine the impact of silencing the neuronal ensembles activated during fear-conditioned learning on memory recall, and we then tested whether the silencing interfered with subsequent relearning in the Tg mice.

RESULTS

The Transgenic System for Reversible Suppression of a Behaviorally Activated Ensemble of Neurons

The neuronal activity-dependent *c-fos*-promoter-driven tTA Tg system permits tagging of specific subsets of neurons that are activated during a behavioral paradigm within a given time