

RESEARCH HIGHLIGHT



Deconstructing the architecture of memory engrams

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Cell Research (2025) 35:783–784; <https://doi.org/10.1038/s41422-025-01179-4>

From “grandmother cell” to engram cells, memory theories have evolved over the last century from finding the engram to deconstructing its internal architecture. Recent studies suggest that engram cells are not uniform, but instead contain subpopulations defined by distinct immediate early genes such as *c-Fos* and *Npas4*; Jin et al. now reveal molecular differences between these ensembles, providing a new molecular perspective on the architecture of memory engrams.

For more than a century, neuroscientists have searched for the physical substrate of memory — the engram. In the early 20th century, Richard Semon proposed that learning leaves behind physical and chemical changes in the brain, forming the basis of memory encoding.¹ Although compelling in its simplicity, engram theory left open critical questions: what are the specific neural substrates, at what scale do they function, and what features define them? By the mid-20th century, the debate shifted to how the brain could represent specific and complex concepts. The most intuitive proposal was the “grandmother cell” theory²: a single neuron dedicated to one specific memory, firing only when that concept was recalled. This extreme version of sparse coding captured the imagination, but proved too simplistic and difficult to demonstrate. At the other extreme, Karl Lashley’s empirical lesion experiments led him to conclude that memory was not localized but distributed across the cortex,³ with no identifiable specific memory cells. These opposing views reflected the limitations of traditional methods and left the mentioned questions unresolved.

The development of recording and labeling techniques gradually overturned the grandmother cell and whole-cortex encoding viewpoints. Over recent decades, memories have been shown to rely on neither single cells nor all cells but on a sparse ensemble of neurons.⁴ The development of activity-dependent genetic labeling systems was a turning point. In particular, *c-Fos*-based labeling tools allow neuroscientists to capture neurons activated during learning and manipulate them subsequently.^{5,6} With these tools, researchers confirmed that activating or silencing a tagged neuronal ensemble was sufficient to induce or block a memory retrieval, providing evidence to support the engram theory.

Yet this progress raised a new question: is the ensemble itself the smallest functional unit, or might it contain finer subdivisions with different functions? Exploration of this question began with a question about whether *c-Fos*-labeled neurons represented the entirety of an engram. Attention soon turned to other immediate early genes (IEGs) that might define additional populations. One of particular interest is *Npas4*, an IEG expressed specifically in the

nervous system. A landmark study showed that in the dentate gyrus — a hippocampal subregion critical for memory encoding — *Npas4*-activated neurons (N-RAM) and *c-Fos*-activated neurons (F-RAM) formed largely non-overlapping ensembles.⁷ More importantly, these two groups played distinct and even opposite roles in memory processes. Subsequent work extended this finding to the amygdala,⁸ further supporting that engram subpopulations activated in parallel can carry fundamentally different functional signatures (Fig. 1).

These findings suggested that engram cells are not homogeneous and they harbor functionally distinct subpopulations. The molecular basis for these differences represents the next milestone in memory engram studies and remains unclear to this day. The new study by Jin et al. provides a crucial piece of this puzzle.⁹ They find that F-RAM cells and N-RAM cells are not redundant copies of the same memory trace but rely on distinct molecular stabilizers. F-RAM cells depend on neuronal pentraxin 1 (NPTX1), which promotes K_v7.2 channel-mediated inhibition to restrain hyperexcitability and ensure successful retrieval of the memory. In contrast, N-RAM cells depend on neuronal pentraxin 2 (NPTX2), which strengthens perisomatic inhibition from parvalbumin⁺ interneurons, thereby preventing memory overgeneralization. Together, these findings reveal differentiated functions within the engram: one subpopulation ensures effective memory retrieval, while the other governs precision. Moreover, the authors showed that both NPTX1 and NPTX2 are selectively down-regulated in engram cells of aged mice. The behavioral consequences paralleled the molecular changes: aged animals exhibited impaired memory retrieval and increased generalization. Remarkably, targeted restoration of these proteins can reverse the deficits, respectively. Overexpressing NPTX1 in F-RAM cells specifically rescued retrieval, while restoring NPTX2 in N-RAM cells alleviated overgeneralization of the memory.

Taken together, these findings offer a molecular perspective on the architecture of memory engrams. The grandmother cell hypothesis is too narrow, while the unitary engram ensemble may be too broad. The present results further support a middle ground: the engram is not a monolithic ensemble but a composite of molecularly distinct submodules, each contributing complementary functions to memory processes.

Although evidence for engram subpopulations is widely accepted and reinforced by the current work, new questions arise. What types of stimuli determine which neurons adopt *c-Fos* vs *Npas4* identities during learning? How do genetically similar neurons within the same region acquire divergent functions? How are distinct subpopulations coordinated into a coherent engram that supports

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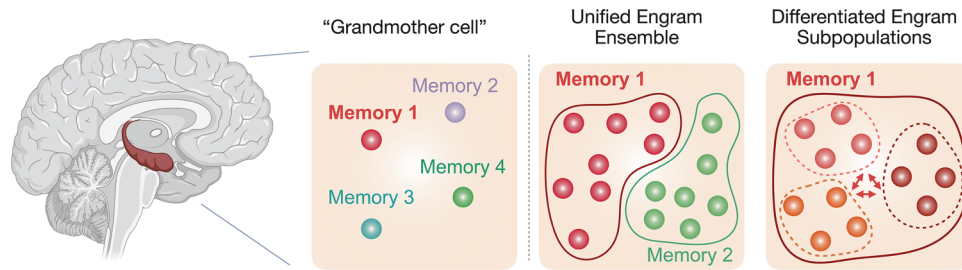


Fig. 1 Three theoretical models of memory encoding. The “grandmother cell” theory represents an extremely sparse and discrete encoding model, where a single, dedicated neuron is responsible for each memory. The initial findings about engram theory demonstrated that memory is encoded by a neuronal ensemble. Recent studies have revealed that such ensembles are not uniform but contain functionally distinct subpopulations, distinguished by different molecular features.

flexible behavior? Are additional IEG-defined submodules yet to be discovered?¹⁰ Addressing these questions will not only refine our understanding of memory engram architecture but also instruct the study of cognitive disorders. The link between selective molecular decline in engram subpopulations and age-related memory impairment suggests that interventions targeting these molecular stabilizers could form a precise therapeutic strategy for neural disorders associated with memory impairment.

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ADDITIONAL INFORMATION

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