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How Does a Memory Find Its Neurons?

Christoph Schmidt-Hieber

How does the brain store and recall memories? We have long known that a brain region called the hippocampus is critical for processing episodic memories. More recently, targeted manipulation of the activity of specific hippocampal neurons in rodents has suggested that memories are encoded by the firing of defined groups of hippocampal neurons, so-called cellular engrams.

In the current issue of BioEssays, França and Monserrat discuss a key question that has puzzled the field for a while: Among the millions of neurons in the mammalian hippocampus, how is a subset recruited into a memory engram?[1] Basic neurophysiology teaches us that two factors largely determine whether a neuron is active: On the one hand, each neuron is excited or inhibited by thousands of synaptic inputs that convey information both about the outside world, and about ongoing processing of information in the brain. On the other hand, how these synaptic inputs will affect the activity of a neuron depends on its excitability, which in turn is determined by factors such as its morphological and biophysical properties.

A straightforward prediction, then, is that an engram is uniquely associated with a specific memory: A given set of sensory stimuli, let's say the odors, colors, and sounds experienced during memory formation, should recruit a given set of neurons – an engram – that is largely predetermined by synaptic connectivity and excitability. Similarly, activating an engram should recall its associated memory, but not others.

Recent experiments in rodents have challenged these straightforward predictions: manipulating the excitability of neurons suggests that there is some redundancy in the hippocampal code, as inhibiting putative future engram cells during memory formation does not inhibit learning of a new memory.[2] Instead, it appears as if the memory could simply be stored in a different population of neurons. From these experiments, one might conclude that hippocampal neurons are stochastically recruited into engrams, and that their initial synaptic wiring plays only a minor role in their selection.[3]

How can the straightforward predictions from basic neurophysiology be reconciled with the seemingly stochastic composition of engrams? França and Monserrat invoke insights into *C. elegans* circuits to argue that individual neurons can represent multiple dimensions of both external and internal variables, most of which escape our observation. While we typically test the purely spatial aspect of memories in rodents, we have relatively little experimental control over variables other than physical space, such as an animal's current goal, attention, or more fundamental sensations such as hunger or thirst. Furthermore, the authors argue that once there is some synaptic distance between the primary sensory inputs and the neurons of interest, these dimensions will be increasingly abstract. Finally, they propose that the apparent redundancy of the code can be explained by the insight that while stimulating two non-overlapping populations of engram neurons may have the same behavioral effect, that does not necessarily mean that the same memory was recalled, as recalling even very different memories may evoke the same behavioral output. Thus, they conclude that the wiring and excitability of hippocampal neurons provides a template for memory allocation, and that the seemingly stochastic nature of engrams can be explained by the notion that hippocampal neurons represent multiple, abstract dimensions.

This is a timely review on a highly interesting topic, and the authors make some novel and creative points about memory allocation. Further work will be required to show whether the striking temporal dynamics of hippocampal representations,[4] which appears to be at odds with engrams determined by hard wiring, are indeed a consequence of varying attentional levels, or whether additional mechanisms such as synaptic turnover may contribute to engram formation.

An important conclusion from their work is that we need better behavioral tasks for animals used in hippocampal research, which are typically rodents. A simple behavior, as tested by a dichotomic go/no-go task, may be the end point of widely different cognitive processes. This redundancy could be reduced if more complex behaviors including multiple choices were tested. More sophisticated behavioral tasks, together with improved control and monitoring of external stimuli and behavioral variables, may therefore disambiguate the effects of stimulating different engrams, and help understand how hippocampal neurons are recruited into memory circuits.

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