A gatekeeper for learning.

Feedback projections from the parahippocampal-hippocampal network control learning processes in the sensory cortex.

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One of the most challenging goals of neuroscience is unravelling the biological underpinnings of cognitive functions. To succeed, a necessary first step is understanding where in the brain cognition arises. In the past decades, the theory has evolved from one by which specific cognitive functions are localized within discrete brain regions, into one where cognition is produced by the coordinated action of interconnected neurons across multiple areas. This is the case for some forms of learning, which might depend on the interplay between the parahippocampal-hippocampal network and the neocortex (*1*). On page **XXX** of this issue, Doron et al. (*2*) reveal that inputs from the perirhinal cortex, one of the parahippocampal areas, modulate the activity of deep-layers pyramidal neurons in the primary somatosensory cortex and control learning.

Learning is a fundamental function of the brain, as it supports the creation of internal representations of past experience that are used to guide future behavior. From a biological perspective, learning strengthens functional connectivity within a subset of co-active neurons, so that this subset of neurons, also known as "neuronal ensemble" or "engram", becomes the biological substrate where a memory is stored (*3*). The interplay between external cues and the engram re-instates the spatiotemporal pattern of activity present during learning, and supports memory retrieval (*4*). It was previously shown that, for some forms of learning, hippocampal activity was necessary for the re-activation of learning-related neuronal ensembles distributed throughout the cortex (*4*). By which mechanisms the hippocampal network influenced the emergence of a brain-wide engram during learning remained however obscure.

To address this question, Doron et al trained rodents to report the artificial microstimulation of their primary somatosensory cortex (S1) by licking for a reward, and showed that learning relied on the activation of both the hippocampus and perirhinal cortex (*2*). Importantly, learning correlated with changes in the activity dynamics of a subpopulation of Layer 5 (L5) neurons in S1. In fact, during successful trials a subset of L5 neurons exhibited increased rates of activity, which was temporally organized in stereotypical patterns of closely-spaced action potentials also known as "bursts". Silencing perirhinal projections to S1 both reduced the fraction of bursting neurons and the animal's success rate in the task.

This observation is in line with a report that engram neurons are more "bursty" than non-engram neurons (*5*), suggesting that bursting might be a physiological signature of memory-bearing cells. How could bursting contribute to learning and memory processes? One possibility is that bursting might increase the reliability of communication between neurons (*6*). In fact, because many central synapses are unreliable and a single action potential often fails to produce a response, a rapid sequence of many action potentials (i.e., a burst) could facilitate synaptic transmission. In this model, bursting might endow memory-bearing ensembles with an efficient, precise, and reliable neural code that allows these neurons to transmit information to downstream readers with high efficacy.

Surprisingly, applying a high-frequency burst stimulation to individual L5 neurons in S1 after learning was sufficient to induce memory retrieval, while a similar number of regular action potentials was not. The stimulated neurons however did not necessarily need to be part of the learning-related ensemble, thus suggesting that bursting of any L5 neuron has the potential to elicit memory retrieval in expert animals – but not in naïve ones. If, upon learning, bursting of any neuron can induce memory retrieval, what is special about engram neurons? Doron et al suggest that even though memory retrieval

naturally relies on the activation of engram neurons, a larger fraction of the network could be involved in the same processes when properly stimulated. Such phenomenon might make retrieval robust to the progressive change in neuronal representations taking place over time in the cortex (i.e., it might make the engram robust to representational drift) (*7*). An alternative hypothesis could be that bursting of a non-engram neuron might re-activate the original engram, possibly through attractor network-based dynamics. Disentangling such hypotheses is left for future investigation.

Since perirhinal inputs target the superficial layers of S1, they might modulate bursting and learning by increasing activity at the apical tuft of L5 neurons dendrites. In support of this, the authors found a fraction of apical dendrites exhibiting large calcium transients upon stimulus presentation after learning. Notably, disrupting apical dendritic activity during learning disrupted performance.

What is the role of apical dendritic activity in learning? Inputs to the neocortex are organized so that distinct information streams terminate within distinct layers (*8*). Feed-forward streams carry information about sensory stimuli and terminate in the middle layers. Feedback streams carry information about context or predictions about the task generated on the basis of an internal model, and impact on the outer layers. Such segregation is reproduced at the level of single L5 neurons, where feed-forward and feedback streams segregate within the basal and apical dendrites, respectively (*8*). The measure in which each information stream shapes neuronal responses might change with learning. At the network level, responses of layer 2/3 neurons align to the feedback instead of the feedforward streams as a result of learning (*9*). Doron at al reveal that perirhinal inputs might act as a gate that modulates apical dendritic excitability during learning, and might enhance the influence of the feedback streams on the activity of L5 pyramidal neurons.

What type of information is carried by the feedback streams, and how this information is used during learning remain unresolved. Some indications might come from the machine learning literature, which postulates that during learning, higher-level information (i.e., the feedback streams) could modulate lower-level activity (i.e, the feedforward streams) towards outputs that are more consistent with the higher-level predictions (*10, 11*). The purpose of this process would be to minimize the difference (i.e., the error) between predicted and obtained outputs – a process that might be central to the inner workings of the brain, too (*12*). Such algorithm, known as "backpropagation of error", is used to train artificial neural networks (*10*). In the future, it will be interesting to understand whether learning-related changes like those observed by Doron et al indeed serve the purpose of calculating errors at the level of individual L5 neurons' dendrites, and drive learning processes in biological neural networks akin to what happens in artificial ones.

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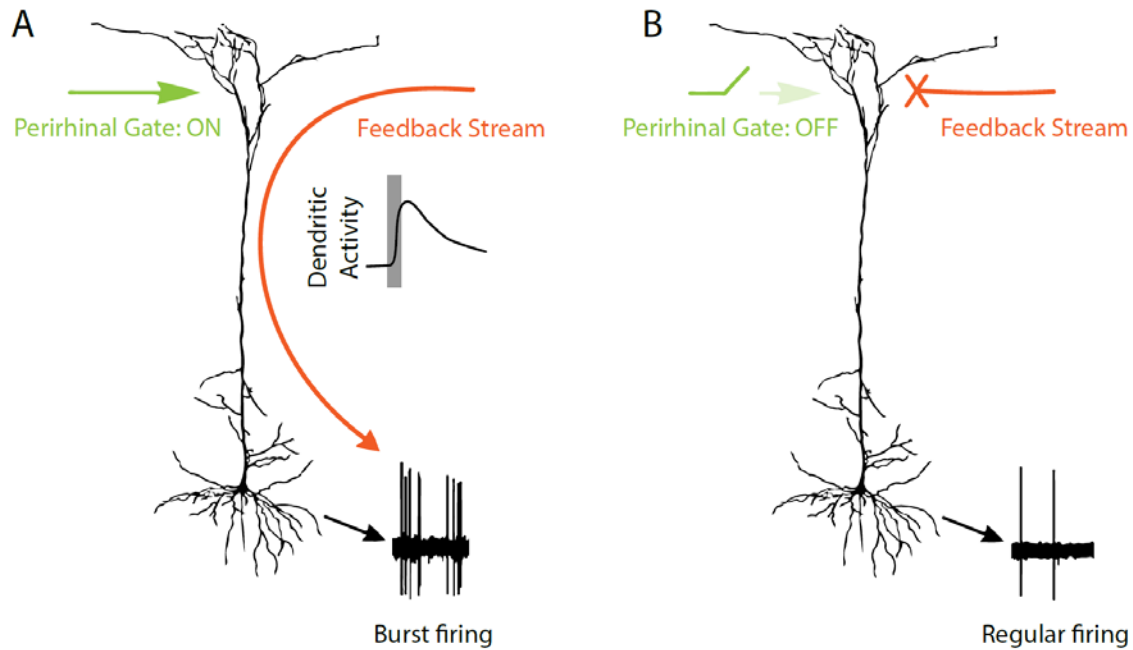
FIGURE LEGEND

Perirhinal-gated dendritic activity supports learning

Upon learning a hippocampus-dependent associative task, perirhinal inputs might act as a gate to modulate the excitability of apical dendrites and the impact of the feedback stream on layer 5 pyramidal neurons of the primary somatosensory cortex. **A**: Perirhinal inputs (gate: ON) supports an increase in apical dendritic activity upon stimulus presentation (grey box), and burst firing in a subset of Layer 5 pyramidal neurons - which correlates with learning and is sufficient for memory retrieval. **B**: Silencing perirhinal inputs during learning (gate: OFF) prevents the emergence of the bursting population, and impairs performance in the task.