The Barista on the Bus: Cellular and Synaptic Mechanisms for Visual Recognition Memory

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Our ability to recognize that something is familiar, often referred to as visual recognition memory, has been correlated with a reduction in neural activity in the perirhinal cortex. In this issue of *Neuron*, Griffiths et al. now provide evidence that this form of memory requires AMPA receptor endocytosis and long-term depression of excitatory synapses in this brain area.

Familiarity and recollection are distinct forms of memory: we can have the sense that we know the man on the bus without necessarily recollecting precisely who he is (Mandler, 1980). Although we may eventually recall that he is the barista who serves us coffee several times a week, our ability to recognize him as familiar does not depend on precise identification. This sense of familiarity, referred to as visual recognition memory, has been the subject of great interest in animal models of learning and memory, as well as in humans.

Ablation studies, analysis of immediate-early gene expression, single-unit response properties, and fMRI imaging in humans have all implicated perirhinal cortex in visual recognition memory (Brown and Aggleton, 2001). Interestingly, studies indicate that object familiarity is linked to a reduction in brain activity in perirhinal cortex, suggesting that a refinement of neuronal ensembles that respond to the visual stimulus occurs during visual recognition memory. This is in contrast to what has been observed in other brain areas, such as the hippocampus, where activation is enhanced for exposure to familiar objects (Montaldi et al., 2006; but see Wais et al., 2006).

The well-defined anatomical locus for familiarity detection makes it an excellent form of memory to begin a more detailed analysis of its underlying molecular mechanisms. Previous data were consistent with the possibility that ensemble refinement occurred through long-term depression (LTD) of synaptic inputs onto neurons in perirhinal cortex. In this issue of *Neuron*, Griffiths et al. (Griffiths et al., 2008) have now carried out a series of elegant and conceptually straightforward experiments that not only link synaptic depression to this form of memory but implicate a specific molecular mechanism—the endocytosis of AMPA-type glutamate receptors (AMPARs)—in this process. Using a modification of a visual recognition task that takes advantage of a rat's preference for novel objects (Figure 1), they investigated how this process could be interrupted by lentivirus-mediated overexpression of peptides that block LTD.

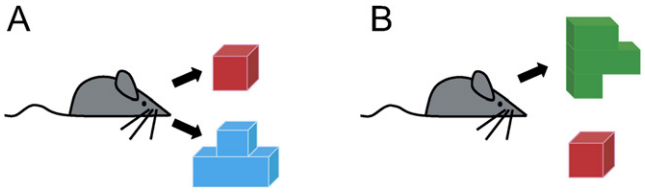

Figure 1. Schematic of Object Recognition Memory Task Used by Griffiths et al.
Animals were placed in an open-topped arena with two different objects composed of "Duplo" (Lego) blocks in a variety of shapes, sizes, and colors in two corners. After some delay, animals were re-exposed to a novel object as well as a copy of one of the first two objects.
(A) At the initial presentation, animals explore both objects equally (indicated by arrows).
(B) Under normal conditions, animals spend more time investigating the novel object (arrow) compared to the previously viewed object.

It is well established that long-term depression of excitatory synaptic responses is mediated by the internalization of AMPARs (Malinow and Malenka, 2002). Receptor endocytosis proceeds by a clathrin-dependent process that links the GluR2 subunit with the clathrin-adaptor protein AP2. Griffiths et al. show first that introduction of a peptide mimic of the AP2 binding domain of GluR2 into the internal solution during whole-cell recording is sufficient to block LTD in acute brain slices. Next, using lentiviruses that express this peptide, they show that bilateral injections of virus into perirhinal cortex (with infection rates of ~60% of all neurons) significantly impair object recognition memory and fully block field potential LTD in acute brain slices from infected animals. Importantly, LTP of excitatory field potentials was not affected by virally mediated peptide overexpression.

These results suggest a mechanism by which presentation of familiar objects results in decreased activity in perirhinal cortex: synaptic depression reduces excitatory drive to neurons and refines (or eliminates) neuronal firing that occurs in response to stimulus presentation. The reduction in population activity may serve as a trigger for familiarity—when fewer neurons fire, this information is transmitted to higher brain areas,

enabling the decision to ignore a familiar object in favor of the novel one. In this way, ensemble refinement may be an essential indicator for familiarity (or novelty) detection, because it appears that preventing synaptic depression is sufficient to eliminate the rat's ability to distinguish novel from familiar objects.

These results do not imply that LTD processes and ensemble refinement are necessary for all types of memory; as mentioned above, other investigators have found that hippocampal activation is not reduced in either visual recognition memory or other types of learning, such as spatial learning. However, there is accumulating evidence that experience or training can result in a similar reduction of stimulus-driven neuronal activity, especially in the neocortex. For example, using a GFP-reporter gene coupled to the immediate-early gene promoter arc, Wang et al. showed that repeated presentations of a horizontal training stimulus refined the population of arc-GFP-expressing cells in visual cortex of transgenic mice, using in vivo time-lapse two-photon imaging (Wang et al., 2006). In this case, the number of arc-GFP-expressing cells decreased with each stimulus training event, and cells that were activated in the final trial were more likely to have been active in earlier trials (Figure 2).

Other studies in primates have also shown that the number of responding units in the neocortex declines with repeated stimulus presentations as animals become more adept at identifying degraded visual images (Rainer and Miller, 2000). And in humans, functional magnetic resonance imaging (fMRI) studies have not only confirmed a role for perirhinal cortex in recognition memory but also have shown the same signal decrement observed by single-unit recording or fos activation in other animals. For example, perirhinal decreases in fMRI signal have been associated with familiarity-based encoding, strength of familiarity at retrieval, and visual recognition learning (Eichenbaum et al., 2007). In one set of studies (Davachi et al., 2003; Ranganath et al., 2004), participants were scanned using fMRI while they encoded (studied) sets of words. Later, subjects underwent memory tests that discriminated among instances of familiarity-based and recollection-based recognition memory. In both studies, perirhinal activity at encoding predicted whether items would later be recognized based on familiarity, but was not predictive of recollection. In all cases, as familiarity with the stimulus set increased, perirhinal activity decreased. It is important to note that, because the blood-oxygen level-dependent (BOLD) fMRI signal reflects local changes in metabolism and circulation (Raichle and Mintun, 2006), a local decrease in signal can be interpreted as a decrease in the energy demand of the neurons in the sample.

With the link between the BOLD response and local metabolic demand in mind, there is also evidence that the strength of the familiarity detection shows a direct and inversely proportional reduction in BOLD fMRI responses in perirhinal cortex. Using visual scenes, Montaldi and colleagues first taught subjects to discriminate among different levels of the strength of familiarity, so, for a given test item, they could differentiate weak (F1) to moderate (F2) to strong (F3) sources of familiarity (Montaldi et al., 2006). At test, they saw old and new scenes and identified which had been studied earlier and which were new. Two findings are particularly relevant here. First, the BOLD response in perirhinal cortex decreased as familiarity strength increased. That is, activity was greatest when test pictures were judged to be weakly familiar (F1) and least when they were strongly familiar (F3; Figure 2). Second, this pattern of response was negative relative to baseline activity, indicating that increases in the strength of familiarity were associated with a suppression of BOLD response.

In vitro analyses of synaptic function after behavioral training have generally found that synapses are strengthened by prior experience, not that there is an overall reduction in synaptic efficacy (Clem et al., 2008; Rioult-Pedotti et al., 2000; Whitlock et al., 2006). These results have supported the notion that LTP is fundamental to experience-driven changes in synaptic function that motivate behavior. Although it is well accepted that LTD processes could, in theory, accomplish signal refinement in the absence of LTP, most of the available experimental data have not supported synaptic weakening as a primary mechanism for learning in the cortex. On the other hand, researchers who use functional imaging have been well acquainted with area-specific activity reductions after learning (Schacter and Buckner, 1998). One strength of the current study is that it implicates a previously underappreciated

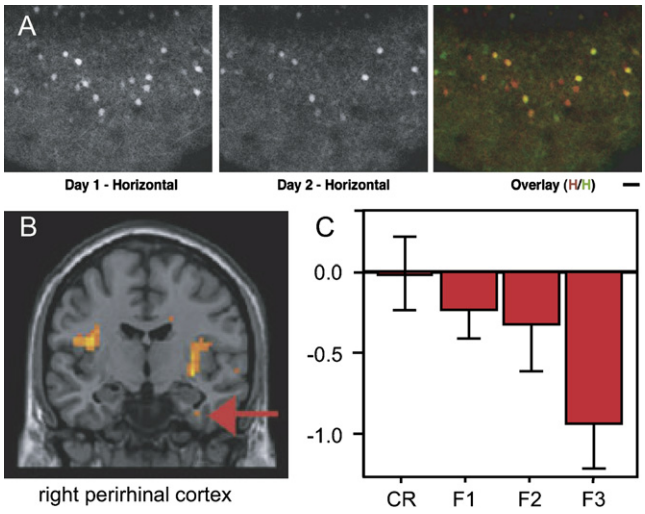

Figure 2. Experience-Dependent Reductions in Neuronal Population Responses

(A) Two-photon in vivo imaging of arc-GFP-expressing neurons in primary visual cortex shows that repeated presentation of a horizontal stimulus reduces the number of reactivated cells indicated by arc-GFP expression. Scale bar, 30 μM. Figure adapted from Wang et al. (2006).

(B) fMRI during a visual recognition memory task shows the location of right perirhinal cortex (orange; denoted by red arrow) superimposed over an anatomical image.

(C) BOLD responses are plotted as a function of task condition. F1-F2-F3 denote increasing familiarity strength associated with correctly identified old scenes. CR denotes new scenes correctly identified as such. On average, the CR condition is associated with less familiarity than the F1-F3 conditions. Responses are in units of percent signal change from baseline. Figure adapted from Montaldi et al. (2006).

molecular process, LTD, in the process of learning and memory in cortical circuits.

These results have broad implications for how learning and decision making are encoded by population responses. LTP and LTD may both be essential in this process: LTD to reduce the activity of cells that are weakly driven by a stimulus and thus constitute some sort of noise in detection and LTP to enhance the responsiveness of a few cells. It remains unknown whether this model holds true in perirhinal cortex—for example, whether LTP is also required for familiarity detection. However, Griffiths et al. have provided some of the first data to indicate what synaptic mechanisms might be at play in *reducing* ensemble responses during familiarity detection. It is unknown what brain area is eventually responsible for the integration of perirhinal signals as well as signals from other brain areas that may be enhanced during visual recognition learning; the question of how information in perirhinal cortex is coded and interpreted will be of considerable interest.

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Cyclic AMP Imaging Sheds Light on PDF Signaling in Circadian Clock Neurons

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In *Drosophila*, the neuropeptide PDF is required for circadian rhythmicity, but it is unclear where PDF acts. In this issue of *Neuron*, Shafer et al. use a novel bioimaging methodology to demonstrate that PDF elevates cAMP in nearly all clock neurons. Thus, PDF apparently exerts more widespread effects on the circadian clock network than suggested by previous studies of PDF receptor expression.

Most animals exhibit circadian rhythms, modulating their physiology and behavior on a 24 hr cycle. Circadian pacemaker neurons (clock neurons) in the central nervous system participate in maintaining circadian rhythmicity. There are ~100–150 clock neurons in insects and 5000–50,000 in mammals. Within individual clock neurons, oscillating expression of clock genes regulates cellular physiology on a 24 hr cycle. Although the phases of transcription vary among clock genes, their frequency typically approximates 24 hr. In consequence, these neurons maintain autonomous rhythmicity even in the absence of external stimuli or feedback from other pacemaker neurons. However, for the clock neurons to effectively modulate the behavior of the animal, they must function in synchrony and entrain to the daily light-dark cycle. Both the mechanisms of autonomous cellular oscillation and of interaction among the clock neurons have been the subject of intensive recent study.

In *Drosophila*, several genes have been identified as clock genes on the basis of their oscillating expression, which is maintained by feedback loops. Two basic helix-loop-helix regulators, *clock* (*clk*) and *cycle* (*cyc*), activate transcription of multiple genes that drive rhythms. Two of these genes, *period* (*per*) and *timeless* (*tim*), form