What does this elaborate series of observations tell us about the mechanism of odor discrimination? One interpretation is that in wild type, saturating levels of one odorant cause a specific downregulation of one odorant response, such that a gradient of a second odorant can be detected. In the mutant that overexpresses ODR-1, however, high levels of butanone signaling downregulate not one but several odor responses. In other words, the normal insulation between butanone signaling and other signaling pathways is compromised. In one version of this model, the downregulation occurs locally in wild-type animals and is effected by localized production of cGMP. In mutants overexpressing ODR-1, high levels of cGMP would result in a more global effect, spreading to downregulate additional pathways. Such a model would fit especially well if olfactory signaling complexes were spatially segregated from one another, as is found, for example, in *Drosophila* phototransduction (Huber et al., 1996; Shieh and Zhu, 1996; Chevesich et al., 1997; Tsunoda et al., 1997). If odor signaling occurs in a discrete complex—an olfactosome, as it were—then cGMP concentration would be highest near stimulated receptors. Thus, L'Etoile and Bargmann speculate that such organization of olfactory transduction components might serve to physically and biochemically insulate different complexes from each other.

Olfactory adaptation is presumably affected by ODR-1 via a different mechanism, since the effect does not require cyclase activity. One possible model is that ODR-1 binds to a protein required for butanone adaptation, titrates it, and thereby blocks adaptation. Perhaps signaling complexes are heterogeneous, such that complexes responding to other odors lack the protein bound by ODR-1 and are not affected by ODR-1 overexpression.

These results invite further experimentation. It will be interesting to determine whether olfactory signaling components in various organisms do in fact cluster in discrete, spatially segregated complexes. As more is learned about the binding specificity of odorant receptors (Zhao et al., 1998; Malnic et al., 1999; Speca et al., 1999; Touhara et al., 1999), it will become more apparent whether competition for receptor binding sites plays any role in odor discrimination in various species, as has been proposed previously (Siddiqi, 1987). It should also be noted that many of the most interesting results from this work come from overexpression studies. Such studies can be enormously illuminating and incisive, but additional insight can often be gained by complementing them with studies of loss-of-function mutations.

Insulation of signaling pathways is likely to be critical not only in *C. elegans* olfactory neurons but also in a wide variety of mammalian neurons, many of which express multiple receptors that converge on common signaling pathways. Thus, our understanding of signaling in many neuronal types may benefit from further consideration of olfactosomes.

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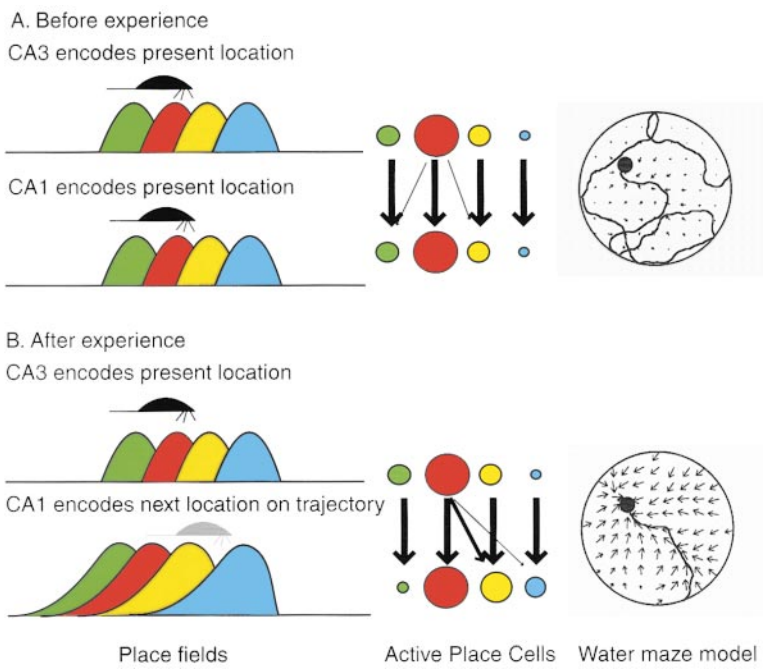
## LTP Takes Route in the Hippocampus

Based on behavioral and lesion data and on the discovery of location-specific place cells in the hippocampus, O'Keefe and Nadel proposed that the hippocampus was the neural substrate of a cognitive map, used not only for navigation but as "an objective spatial framework within which the items and events of an organism's experience are located and interrelated" (O'Keefe and Nadel, 1978, p. 1). Place cells are hippocampal principal cells whose firing rate increases when the animal is at a particular location—the "place field"—in its environment (O'Keefe and Dostrovsky, 1971). The functional properties of these cells have long been a source of fascination for cognitive scientists, as they would appear to provide an important inroad into how learning and memory is encoded. Most research on place cells has focused either on the determinants of their spatial tuning (Redish, 1999) or on the extent to which they encode nonspatial information (Cohen and Eichenbaum, 1993). Although a number of theoretical models have been proposed to explain how place cells might control navigation, little experimental data exist to test these models. In this issue of *Neuron*, Mehta et al. (2000) present data that confirm the predictions of a certain subset of these models. While these results do not by themselves prove the validity of the models, they demonstrate a powerful approach to testing the predictions of models based on population analyses of neuronal ensemble data.

Mehta et al. recorded ensembles of place cells as rats made stereotyped linear trajectories. An earlier paper reported that, on average, place fields on such linear tracks became larger with experience and shifted backward, opposite to the direction of motion of the rat (Mehta et al., 1997). In the current paper, the authors




Changes to Place Fields with Experience

The size of the circles representing active place cells is proportional to the firing rate, and the line thickness is proportional to synaptic strength. The water maze model is reproduced with permission from Blum and Abbott (1996).

build on this earlier study, which examined the average behavior of populations of neurons, to track what happens on a cell-by-cell basis, and they show that the shapes of individual place fields became skewed over the first five to six laps on each day of recording. The direction of the skew was found to be opposite to the stereotyped path of the rat and thus could potentially explain both the place field expansion and the backward shift demonstrated earlier.

How might experience cause such changes in place fields? The authors reasoned that one potential explanation might involve long-term potentiation (LTP) at these hippocampal synapses. To explore this possibility, the authors modeled changes in place field shape using a network that incorporates temporally asymmetric LTP between CA3 and CA1. Since LTP is induced between two neurons if the presynaptic neuron is active before the postsynaptic neuron, but not vice versa (Levy and Steward, 1983), synapses between a given place cell and its afferent place cells that fire slightly *earlier* should be enhanced selectively over synapses between that cell and its afferent cells that fire *later*. Thus, before experience, both CA3 and CA1 encode the current location of the rat in the model (i.e., the red place cells fire strongly when the rat is centered in the red "place field") (see panel A in figure). After repetitions of the green–red–yellow–blue trajectory, however, the temporal asymmetry of LTP induction causes an asymmetric strengthening of connections between the CA3 and CA1 place cells. After experience, when the rat is at the same location as before, the newly strengthened connections between the red CA3 cell and the yellow and blue cells in CA1 cause the latter cells to also fire moderately. As a result, the CA1 place fields shift backwards, and the population activity in CA1 now encodes a location slightly ahead of the rat, corresponding to the rat's previously experienced trajectories (see panel B in figure).

In support of the idea that changes in receptive field properties may involve NMDA-dependent LTP, preliminary reports by Mehta and McNaughton (1997, Soc. Neurosci., abstract) and Ekstrom et al. (1999, Soc. Neurosci., abstract) claim that NMDA receptor blockers eliminate or reduce the place field expansion and backward shift. In addition, while only a correlation, it is interesting to note that the effects of place field expansion have been found to be reduced in aged rats, which generally have deficiencies in LTP and in spatial learning (Shen et al., 1997). If these associations between LTP and the effects reported by Mehta et al. hold true, then it adds another important clue into the functions of LTP in the hippocampus. Kentros et al. (1998) recently showed that blocking LTP does not affect place field expression per se, but blocks the maintenance of a stable representation of a novel environment over subsequent exposures to that environment. The present results suggest an additional role for LTP, but it remains to be determined where in the brain these effects really occur and it will be necessary to experimentally tie these results to LTP in different subfields of the hippocampus. For example, it could be that LTP in CA3 is responsible for one effect, whereas LTP in CA1 or dentate gyrus may be responsible for another (or even that the effects are due to LTP-dependent changes upstream from the hippocampus).

These results also have relevance to recent computational models of place cells, including models of route learning, sequence learning, and theta phase precession (for references, see Mehta et al., 2000). For instance, Blum and Abbott (1996) incorporated temporally asymmetric LTP in a goal finding/navigation model in which the rat learns the Morris water maze task. As the model rat learned the task, shifts in the locations of place fields generated a map of potential routes toward the goal. In the figure, panel A (right) shows the state of their model

at the beginning of training, when there is little information encoded in the map. At the end of training (see panel B [right]), the map now encodes the directions at each location that incrementally lead to the hidden platform. The observations made by Mehta et al. in the current paper suggest that such a representation may be encoded in the hippocampus. However, it is not yet known how such a representation would be read out and translated into the motor commands necessary for the rat to follow the route(s) laid out in this map, and there is as yet no evidence that the effect seen by Mehta et al. is actually related to goal finding. A potential means of addressing these issues would be to record multielectrode data on a navigational task similar to the Morris water maze. One predicts that place fields would be symmetric as the rat initially learns the task, but after training place fields would be skewed in a direction away from the general direction toward the learned goal location.

Mehta et al. also suggest that these results may have broad relevance to cortical receptive fields in general. Indeed, these results may offer insight into how stereotyped or repeated behaviors or perceptual experiences, such as in reading, skill learning, or enduring thousands of trials in a psychophysics experiment, are encoded and ultimately translated into the increased motor or perceptual performance associated with such tasks (Abbott and Blum, 1996). It might therefore be interesting to look for effects similar to those demonstrated by Mehta et al. in visual or motor cortex. The discovery of such general effects could elucidate a key mechanism by which neuronal populations learn sequences of neural firing patterns that underlie a multitude of perceptual and skill-learning processes.

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