

will behave as a rigid system—the system will be jammed (10). Studies of jamming in collections of spherical particles have uncovered many aspects of the rich structure of these disordered systems (11–14). Despite the absence of nematic order, these systems show swirling near the jamming transition (see the figure). Probing the spatial ordering and mechanical properties of nematic particles, such as ellipses, promises to provide fresh insights into swarming and jamming.

Does the transition to swarming precede the jamming transition or coincide with it? Do giant fluctuations persist near jamming? Are swarming and swirling two manifestations of

the same underlying mechanism? To answer these questions, physicists will increasingly subject rice grains, rods, needles, disks, and other nonspherical objects to shaking and shearing in the coming years. What is clear already is that shape matters.

#### References

1. V. Narayan, S. Ramaswamy, N. Menon, *Science* **317**, 105 (2007).
2. T. Vicsek, A. Czirok, E. Ben-Jacob, I. Cohen, O. Shochet, *Phys. Rev. Lett.* **75**, 1226 (1995).
3. I. D. Couzin, J. Krause, N. R. Franks, S. A. Levin, *Nature* **433**, 513 (2005).
4. J. Toner, Y. Tu, *Phys. Rev. E* **58**, 4828 (1998).
5. S. Ramaswamy, R. A. Simha, J. Toner, *Europhys. Lett.* **62**, 196 (2003).

6. H. Chaté, F. Ginelli, R. Montagne, *Phys. Rev. Lett.* **96**, 180602 (2006).
7. V. Narayan, N. Menon, S. Ramaswamy, *J. Stat. Mech.* **2006**, P01005 (2006).
8. I. S. Aranson, D. Volfson, L. S. Tsimring, *Phys. Rev. E* **75**, 051301 (2007).
9. A. Donev *et al.*, *Science* **303**, 990 (2004).
10. A. J. Liu, S. R. Nagel, *Nature* **396**, 21 (1998).
11. O. Dauchot, G. Marty, G. Biroli, *Phys. Rev. Lett.* **95**, 265701 (2005).
12. A. S. Keys, A. R. Abate, S. C. Glotzer, D. J. Durian, *Nature Phys.* **3**, 260 (2007).
13. W. G. Ellenbroek, E. Somjai, M. van Hecke, W. van Saarloos, *Phys. Rev. Lett.* **97**, 258001 (2006).
14. F. Lechenault, O. Dauchot, G. Biroli, J.-P. Bouchaud; available online at <http://arXiv.org/abs/0706.1531v1>.

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## NEUROSCIENCE

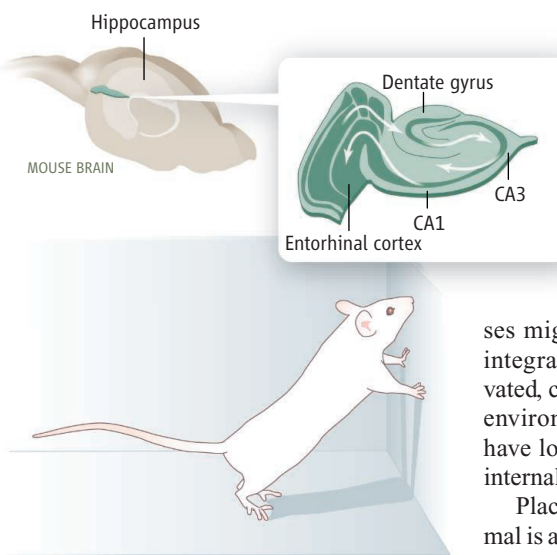
# Remembering the Subtle Differences

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A good taxi driver in a cosmopolitan city has to find an arbitrary destination from any starting point, efficiently and with high precision, relying on recollection of the city's layout and taking into account changes in traffic or road conditions. The hippocampus is central to such tasks that rely on memory and spatial navigation, and the way in which it does this is a key issue in neuroscience. Over more than a decade, the Tonegawa laboratory has analyzed the function of neuronal plasticity in the rodent hippocampus by selectively altering the expression of genes associated with the function of synapses, the junctions that facilitate communication between neurons (1, 2). On page 94 of this issue, McHugh, Tonegawa, and colleagues (3) identify an important role for synaptic plasticity in the dentate gyrus of the hippocampus for learning. The findings explain how we detect small changes in our environment, perhaps allowing us to update and guide our choices.

The principal excitatory neurons of the mammalian hippocampus are organized into three different cell layers that are linearly connected. The entorhinal cortex, which provides the major input of sensorial information to the hippocampus, sends activating

signals to the granule cells of the dentate gyrus (see the figure). The dentate gyrus, in turn, sends neuronal projections (axons) to CA3 hippocampal cells. CA3 neurons project to CA1 pyramidal cells, thus establishing



**Knowing what, when, and where.** In the mouse brain, the dentate gyrus region of the hippocampus can detect small changes in the animal's spatial environment and differentiate between recent experiences that occur in the same place. The white arrows trace a path of signaling between different regions of the hippocampus. Sensory information can enter the hippocampus from the entorhinal cortex and is sent back to the entorhinal cortex after processing.

Mice use a specific neurotransmitter receptor in the dentate gyrus of the hippocampus to detect small changes in their surroundings and differentiate between similar experiences.

a “trisynaptic” pathway in the hippocampus. To complete the circuit, CA1 cells send output signals back to the entorhinal cortex. In addition to this major trisynaptic pathway, there are connections between CA3 cells and additional entorhinal cortical inputs onto both CA3 and CA1 cells. Synaptic strengths at each node in the trisynaptic pathway can be modulated, and this is partly dependent on the *N*-methyl-D-aspartate (NMDA) receptor, which is activated at synapses by the neurotransmitter glutamate. Altering the strength of individual synapses might enable hippocampal neurons to integrate into ensembles that, when activated, could represent salient features of the environment. Hippocampal “place” cells have long been taken as evidence for such internal representations (4).

Place cells are active only when the animal is at a particular position in space. These neurons could therefore identify the animal's current spatial location and, in concert with other neuronal ensembles, track the animal's movement. But beyond spatial information, hippocampal neuronal activity may provide a more complete representation of episodes or experiences (5, 6).

Distinct features of hippocampal activity—its so-called neuronal code—are differentially sensitive to small and large changes

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in environmental or contextual features, suggesting that there are multiple mechanisms by which experiences can be differentiated (7, 8). Small changes in contextual cues result in a change in the correlated neuronal activities (“rate remapping”) in the dentate gyrus and CA3, whereas larger changes in contextual information result in the recruitment of different neurons, especially in CA3 (“global remapping”) (8). McHugh *et al.* observed that rate remapping, but not global remapping, was disrupted in mice genetically engineered to lack NMDA receptors in the dentate gyrus (lack of a functional receptor prevents changes in synaptic strength). This phenotype allowed the authors to assess the role of rate remapping in differentiating between similar experiences.

McHugh *et al.* used a modified fear conditioning paradigm in which one of two experimental contexts to which mice are exposed was paired with the animal receiving a footshock. Although mice lacking NMDA receptors in the dentate gyrus acquired and retained contextual fear conditioning—the animals learned to associate fear with a particular environment—they were slower compared to wild-type littermates in learning to discriminate between two similar contexts. This result is consistent with the idea that synaptic plasticity at entorhinal cortex–dentate gyrus synapses is important when spatial context is used to identify the appropriate memory (receiving a footshock or not), and subsequently for making the appropriate behavioral response (whether or not to become immobile) (9). This notion has often been considered in terms of an ability to recall “what” happened “where,” and could make a key contribution to episodic memory in humans. The NMDA receptor-mutant mice could, however, acquire spatial memory when learning to navigate a watermaze. The clear implication, therefore, is that NMDA receptor–dependent spatial pattern separation in the dentate gyrus is not required to solve the watermaze. So when is pattern separation a key feature of hippocampal function?

McHugh *et al.* show that subtle changes in the spatial context are sufficient to require pattern separation, but are such context shifts necessary? In a similar study, mice lacking NMDA receptors in the dentate gyrus learned to discriminate between which arms of a radial maze contain food rewards and which arms are not rewarded: They acquired spatial “reference” memory, as did the mice in the watermaze experiment (10). However, the mutant mice could not

keep track of which arms they had already visited, making more spatial “working” memory errors than wild type mice with intact dentate gyrus physiology. The requirement for spatial pattern separation is the same for both the reference and working memory components of this task. Therefore, impaired spatial pattern separation cannot explain this spatial working memory deficit.

To solve a spatial working memory task, an animal must also process the temporal context associated with an event (“what happened, and when”) and record or represent which locations have been visited recently. A role for the hippocampus in encoding temporal sequences in rodents has been demonstrated (11). Now, the new studies with genetically modified mice show that NMDA receptor–dependent plasticity at synapses in the dentate gyrus, and the possible subsequent rate remapping of correlated neural activities, contribute to temporal information processing, providing a mechanism by which recent experiences could be represented and thus differentiated.

The development of mice with inactivated or activated genes in specific regions

of the hippocampus constitutes a great step forward in our understanding of how the hippocampus works. The challenge now is to understand the roles of individual NMDA receptor subunits, different forms of synaptic plasticity (long-term potentiation, long-term depression, and depotentiation), and the various hippocampal subregions (dorsal-posterior and ventral-anterior) in regulating behavior.

#### References

1. J. Z. Tsien, P. T. Huerta, S. Tonegawa, *Cell* **87**, 1327 (1996).
2. K. Nakazawa *et al.*, *Science* **297**, 211 (2002).
3. T. J. McHugh *et al.*, *Science* **317**, 94 (2007); published online 7 June 2007 (10.1126/science.1140263).
4. J. O’Keefe, L. Nadel, *The Hippocampus as a Cognitive Map* (Clarendon, Oxford, 1978).
5. E. R. Wood, P. A. Dudchenko, H. Eichenbaum, *Nature* **397**, 613 (1999).
6. S. Leutgeb *et al.*, *Science* **309**, 619 (2005).
7. S. Leutgeb, J. K. Leutgeb, A. Treves, M.-B. Moser, E. I. Moser, *Science* **305**, 1295 (2004).
8. J. K. Leutgeb, S. Leutgeb, M.-B. Moser, E. I. Moser, *Science* **315**, 961 (2007).
9. R. Hirsh, *Behav. Biol.* **12**, 421 (1974).
10. B. Niewoehner *et al.*, *Eur. J. Neurosci.* **25**, 837 (2007).
11. N. J. Fortin, K. L. Agster, H. B. Eichenbaum, *Nature Neurosci.* **5**, 458 (2002).

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## CANCER

# Sex, Cytokines, and Cancer

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A cell signaling protein associated with the innate immune response is linked to a pathway that supports cancer progression.

Cancers are not just malignant cells. More than half of the cancer mass can be made of supporting cells such as fibroblasts, tissue macrophages, and endothelial cells; cancers cannot progress into life-threatening metastatic lesions without them. The process by which normal cells are recruited, expanded, and maintained in cancers is closely related to inflammation and to the remodeling that occurs in tissues as the damage of acute inflammation is repaired (1). Two papers in this issue, by Naugler *et al.* on page 121 (2) and Rakoff-Nahoum and Medzhitov on page 124 (3), advance our understanding of the mechanisms of cancer-related inflammation. They describe an important role for an intracellular signaling protein called MyD88

in the development of experimental liver and colon cancers in mice. MyD88 function has been well characterized in the innate immune response (4), relaying signals elicited by pathogen-associated molecules and by the inflammatory cytokine interleukin-1 (IL-1). Its identification in promoting cancer progression reveals a molecular pathway that could be targeted for drug development.

Early experiments demonstrated the need for inflammatory cytokines such as tumor necrosis factor- $\alpha$  (5), and inflammatory cells such as macrophages (6), in the development and spread of some experimental tumors. More recently, activation of the transcription factor nuclear factor  $\kappa$ B (NF- $\kappa$ B), which is critical in cellular responses to TLR ligands and IL-1, was implicated in the innate immune response promoting murine hepatocellular and colon carcinoma (7, 8). The conclusion from Naugler *et al.* and Nahoum and Medzhitov is that MyD88 may function upstream of NF- $\kappa$ B in cells

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