Philippine Archipelago, where more than 500 species of reef-building corals can be found in the same area. Many coral species are very difficult to identify to the species level in the field. Additionally, further taxonomic and/or genetic studies are needed to determine the validity of a large number of reef-building coral species, especially those in the family Acroporidae (*7*).

The study by Gilmour *et al*. prompts us to ask how many of the world's reef systems are as isolated from anthropogenic impacts as Scott Reef, and to what degree they are benefiting from local recruitment. What will be the impact of increased ocean temperature and acidification on the long-term survival of all reefs, especially as even isolated reefs are susceptible to climate-driven reef degradation (*14*)? Across all coral reef ecosystems, more research is needed on which species are more resilient to local or global threats and which species are at highest risk of little or no recovery.

Without more comprehensive species-specific information and research, it remains unclear whether coral species composition and regeneration in recovered reefs can ever reach the same state of previously healthy, undisturbed reefs. It is clear, however, that substantially reducing anthropogenic impacts on coral reefs might at least buy us, and coral reef ecosystems, more time to answer these questions.

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NEUROSCIENCE

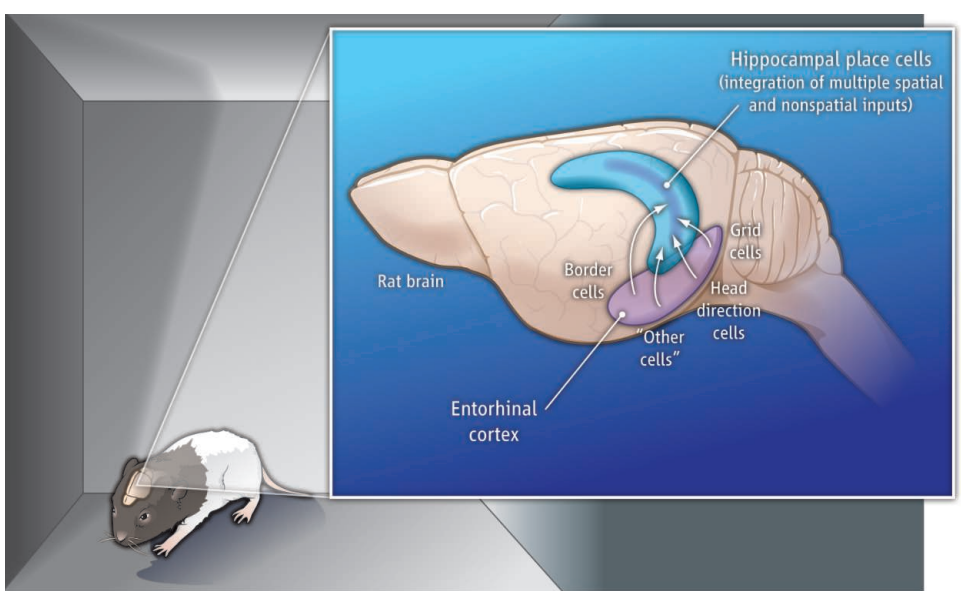
A Trace of Your Place

Multiple signals of different cellular origin in the brain's cortex must be integrated in a single cell type in the hippocampus to assess spatial location.

Bruno Poucet and Francesca Sargolini

How do you know where you are? How do you generate or remember a mental map of your surroundings? Spatial cognition arises from multiple neural systems in the brain that converge to provide this awareness. Teasing out the origin of brain signals that course through these networks is tremendously difficult because the number and nature of pathways in the brain that give rise to a particular signal—the afferent inputs—are often not known. This becomes even more complicated if one looks for connectivity along these pathways at the level of single neurons, the most elementary operating units in the brain, because of the thousands of connections a neuron can make with other neurons. On page 44 of this issue, Zhang *et al*. (*1*) tackle this question by identifying the afferent cells in the entorhinal cortex—a region associated with navigation and memory—that send signals to the hippocampus, specifically to "place cells," neurons that become active in response to a specific location in an environment. The scheme that emerges establishes functional connectivity at an unprecedented level of detail.

The study of spatial cognition has benefited from experimental paradigms that can be made relevant to humans or animals, such as rodents. It has been known for more than 40 years that when rats freely move in a small arena, pyramidal cells (a type of hippocampal neuron) show a peculiar activity—certain cells "fire" (send an electrical signal) when the animal is in a specific area. These pyramidal cells are "place cells" (*2*), and the ani-



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Mental map of location. The hippocampus in both humans and rats is involved in spatial awareness and navigation. All cell types in the medial entorhinal cortex (rat shown) project to place cells in the hippocampus. These inputs include cells with strong spatial correlates (grid cells, border cells, and head direction cells), but also cells with much weaker or no spatial signal. How these signals are all integrated to give rise to the place cell signal remains an unresolved issue.

Laboratory of Cognitive Neuroscience, CNRS–Aix Marseille Université, 13331 Marseille Cedex 3, France. E-mail: bruno.poucet@univ-amu.fr

mal's particular location in a particular environment that activates specific place cells is called the "place field." There does not appear to be a topographical relationship between the anatomical location of the cells within the hippocampus and the place fields of these cells in an environment. Multiple cues are thought to contribute to a place cell's activity such as external landmarks and the animal's own motion (*3*). However, the underlying neural circuitry responsible for generating a place field is still a matter of debate. Because the vast majority of cortical inputs to the hippocampus stem from the entorhinal cortex, it is plausible that information about both external cues and self-motion is relayed by entorhinal neurons. This hypothesis has received strong support from the discovery of grid cells (*4*) in the medial entorhinal cortex. Grid cells resemble place cells in that they display location-specific firing and process both external landmarks and self-motion cues (*5*). However, in contrast to hippocampal place cells (which usually have a single place field in a given environment), grid cells fire at multiple locations in a very regular grid-like pattern. Given that grid cells directly project to the hippocampus, it is tempting to hypothesize that place cell signals may result from the convergent input from several grid cells, with the integration of grid cell activity by place cells obeying sophisticated transformation rules. More recent research, however, has revealed that the medial entorhinal cortex also contains cells that code the animal's head direction (*6*) or the presence of borders in the environment, as well as other cell types that carry a weak spatial signal or no spatial signal at all (*7*). All of these different types of cells could potentially influence place cell activity or even contribute to the generation of their location-specific signals.

To characterize the precise functional anatomical connections between the entorhinal cortex and hippocampal place cells, Zhang *et al*. combined optogenetic activation of single neurons and electrophysiological recording of the same neurons in freely moving rats. A recombinant adeno-associated virus was engineered to deliver a gene encoding an ion channel that is sensitive to light. When injected into the hippocampus of the animal, the viral vector was taken up by the axons of the neurons in the entorhinal cortex that project to the hippocampus. When stimulated by light, these neurons could be activated and therefore be identified according to their electrophysiological signature. Parallel recordings of the same projecting neurons were taken while the animal freely explored an arena, allowing measurement of the spatial information carried in these neurons. Thus, this method enables characterization of the cortical signals that give rise to the activity of hippocampal place cells.

Surprisingly, Zhang *et al*. report that all cell types in the medial entorhinal cortex were tagged with approximately equal proportions by this technique, indicating that place cell activity results from convergent input signals from several functional cell types. Thus, it is unlikely that place fields result from a simple summation of several converging grid cell fields or any other specific signal from the medial entorhinal cortex. This makes sense, given the major properties of place cells. For example, place cells usually discharge regardless of the animal's head direction in open environments, and their activity is controlled by visual cues but remains unchanged in total darkness. These features reflect the highly integrative nature of their signal, which is possible only if they receive a wide variety of inputs.

The findings raise numerous questions about how place cells combine the different signals to generate a reliable place field. Perhaps place cells receive different inputs from the medial entorhinal cortex. It will also be interesting to determine whether there are different categories of place cells according to the type of input they preferentially gate. The answers should guide our understanding of the origin of the place-selective signal of place cells, which remains an open question, and help us to understand how humans, whose hippocampus also contains place cells (*8*), form a mental map of the environment.

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PHYSIOLOGY

The Perfect Hypnotic?

A compound that blocks a neurotransmitter receptor is the newest hope for getting a good night's sleep without the bad side effects.

Emmanuel Mignot

The market for hypnotics is big business, with 10 to 15% of the population in the United States suffering from chronic insomnia (*1*, *2*). Although the pathology is unknown, and likely heterogeneous, patients with insomnia are in a state of hyperarousal (even during the day), suggesting that wake-promoting systems are hyperactive (*3*). The search for the ideal hypnotic has been marked by cycles of exuberance followed by disappointment, as adverse side effects associated with each new class of drug have emerged following wide use. Although insomnia therapy increasingly uses cognitive behavioral therapy, the enormous number of sufferers mandates new pharmacological approaches. Uslaner *et al*. (*4*) report the prospect of a new class of compound with a new mode of action that may usher in a new era for insomnia treatment, with the potential for fewer side effects.

At the beginning of the 19th century, chloral hydrate, meprobamate, and barbiturates were touted as nonaddictive miracle tranquilizers, but in the 1950s, their potential for tolerance and severe addiction was recognized (*5*). At high dose, they lead to pulmonary arrest and death, outcomes that gained further notoriety with the deaths of celebrities Marilyn Monroe and Jimi Hendrix. Broad inhibition of brain activity through high-dose barbiturates can even induce a "flat" electroencephalogram mimicking brain death. Barbiturates activate a chloride channel receptor for gamma-aminobutyric acid [type A ($GABA_A$)]. GABA is the main inhibitory neurotransmitter, produced by 15 to 20% of all brain neurons.

Hope for a safe, effective hypnotic reemerged with chlordiazepoxide, the first benzodiazepine [(BDZ); a two-benzene ring structure linked by a third, diazepine ring].

Center for Sleep Sciences, Stanford University, Palo Alto, CA 94304, USA. E-mail: mignot@stanford.edu