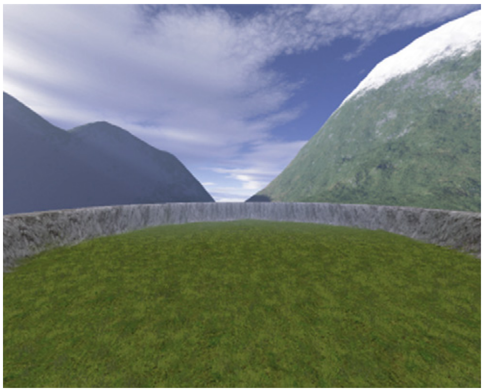
Neurobiology Select

Ongoing efforts to link patterns of neural activity to cognition and behavior entail the use of an impressive range of techniques, from single-cell recording to functional magnetic resonance imaging. Recent discoveries in systems neuroscience, highlighted in this issue's Neurobiology Select, include evidence that humans use grid cells for spatial navigation and a report linking small variations in membrane potential, known as spikelets, to spatial representations in the hippocampus of the rat. Other advances implicate theta wave synchronization between distant brain regions in anxiety behavior and suggest that the degree of correlated firing in cortical microcircuits may be much lower than previously thought.



Human participants explored a virtual reality environment while lying in a functional magnetic resonance imaging (fMRI) brain scanner. Image courtesy of C.F. Doeller.

Human Spatial Memory Gets on the Grid

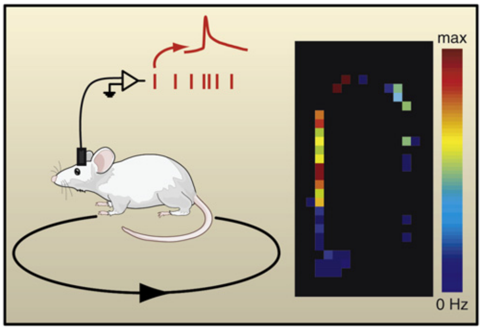
In the rat and mouse entorhinal cortex, the firing of particular neurons known as grid cells shows a distinctive pattern of activity as an animal freely explores its environment. When the occurrence of firing of a grid cell is placed on a map of the animal's location, what emerges is a triangular grid, with peak activities at the vertices. By cleverly taking advantage of the unique collective properties of grid cells, Doeller et al. (2010) now provide evidence that humans also have and use grid cells during navigation tasks. The authors imaged neural activity using functional magnetic resonance imaging (fMRI) of participants as they explored a virtual landscape. Because of the six-fold symmetry of the activity map of the population of grid cells, the modulation of firing of some grid cells by running direction, and the fact that grid cell activity is more pronounced at faster running speeds than at slow speeds, the authors predicted how neuronal activity should vary as a function of the speed and direction of a participant's virtual exploration. The authors observed these predicted activation patterns with the most pronounced signature of grid cell activity found in the human entorhinal cortex. In a larger context, these efforts demonstrate the potential of fMRI to infer the fine-scale properties of neural networks in humans by building on animal models where, unlike in humans, it is possible to measure the activity of individual neurons.

C.F. Doeller et al. (2010). Nature ***463****, 657–661.*

Spikelets Rev up Neuronal Engines

Spikelets are variations in the membrane potential that are much smaller than the action potentials that mediate neurotransmission. Long appreciated, but little understood, work by Epsztein et al. (2010) now suggests that spikelets do not occur randomly but appear to contribute in a systematic fashion to neural representations of space and have a role in driving full-blown action potentials. The authors make intracellular recordings from individual place cells of the rat hippocampus to measure spikes and spikelets as the animals freely explore an O-shaped maze. Place cells get their name from their propensity to fire at a higher rate when an animal is at a particular location in its environment. The authors show that spikelets in individual neurons occur more frequently in a particular location of the animal's test environment as has previously been shown for spikes. Moreover, they report that spikelets contribute to nearly a third of all action potentials in this class of neurons. Future work may further explore what instigates spikelets and why some occur in isolation whereas others occur in bursts.

J. Epsztein et al. (2010). Science ***327****, 474–477.*

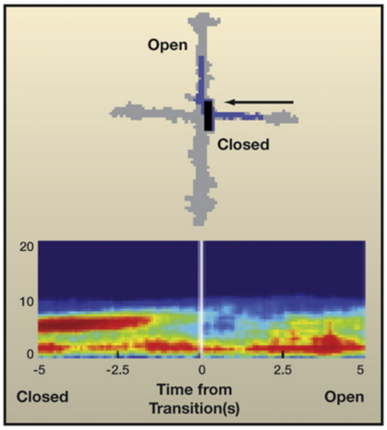


The spatial modulation of spikelet occurrence as shown by a color-coded rate map is revealed by intracellular recording of hippocampal place cells in freely moving rats. Image courtesy of J. Epsztein.

Theta Wave Analysis Reveals a Worrisome Trend

The hippocampus is a region of the brain that is critical for anxiety-related behaviors. Working in mice, Adhikari et al. (2010) provide new insight into how the hippocampus communicates with downstream brain regions that affect behavioral outcomes to anxiety-provoking stimuli. The authors analyze theta rhythms (an oscillating pattern of neural activity with a frequency that typically ranges between 4 and 12 Hz) in mice exposed to stimuli that promote anxiety, in this case an open field test or an elevated plus maze. They show that the theta rhythms of the ventral hippocampus of mice are synchronized with those that occur in the medial prefrontal cortex under normal conditions, suggesting that there is an active channel of communication between the two brain regions. This correlation is further strengthened by stimuli that provoke anxiety behaviors, suggesting that the two brain regions are functionally interconnected. Prior work has linked the medial prefrontal cortex to the modulation of anxiety, in part due to its interconnectivity with brain regions involved in fear memory, such as the amygdala. In the current study an increase in the theta power (measured in mV^2/Hz) of the medial prefrontal cortex predicts when the mice will go to the enclosed arm of the elevated plus maze, that is, the "safe" area. Likewise, a decrease in theta power foreshadows when the mice risk venturing into the anxiety-provoking open arm of the maze. The authors further show that mice deficient in serotonin 1A receptor, which are known to display increased levels of anxiety, exhibit a concomitant increase in theta power in the medial prefrontal cortex compared to wild-type animals that are exposed to identical anxiety-provoking stimuli. Future work may reveal additional molecular players in the hippocampus and medial prefrontal cortex that modulate theta wave power in this experimental paradigm.

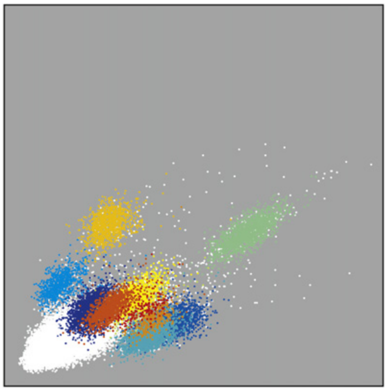
A. Adhikari et al. (2010). Neuron ***65****, 257–269.*



A decrease in theta-frequency power in the medial prefrontal cortex predicts when mice will venture from the safe, closed arm to the aversive, open arm in an elevated plus maze. Image courtesy of J. Gordon.

Neighbors Display Surprising Individuality

Spike recording has frequently revealed a substantial degree of correlated firing among neighboring cortical neurons, which has been thought to result from shared inputs and to reflect the organization of the cortex into functional columns. However, recent reports by Ecker et al. (2010) and Renart et al. (2010) suggest that spiking correlations can be much weaker than previously thought, by as much as an order of magnitude. Suspecting that uncontrolled variables might account for the observations in the existing literature, Ecker et al. reassessed the question adding further experimental safeguards. These include conducting their measurements in awake macaques to avoid spontaneous oscillations that sometimes occur with anesthesia, the use of implanted tetrodes for their recording rather than electrodes whose position might become inadvertently moved, and recording from a brain area whose input could be readily regulated experimentally. For the latter they selected the primary visual cortex, the first cortical area to receive visual information from the thalamus, and measured the activities of neuronal ensembles while the macaques looked at defined visual stimuli. This analysis shows that the spiking of neighboring neurons has almost no correlated variability, suggesting that either the degree of shared input is less than previously thought or that there is some active process at work to uncouple the activity of neighboring neurons.



Colored clusters show peak-to-peak amplitudes of multiple neurons recorded simultaneously from primary visual cortex of an awake macaque using chronically implanted tetrodes. Image courtesy of A. Tolias.

The findings of Renart et al. also call into question prior assumptions concerning the observed correlation in the spiking of neighboring neurons. Their analysis of rat neocortex largely resonates with the report of Ecker et al., showing almost no correlation in firing among groups of neurons in activated states of sustained firing. They further provide a theoretical underpinning for this newly discovered phenomenon, suggesting that the observed low degree of correlation could result from an active process that is inherent in the architecture of cortical networks. Their modeling indicates that the effect of shared input for a pair of neurons can be counteracted if the fluctuations in activity in their presynaptic excitatory and inhibitory inputs are themselves correlated and show that excitatory-inhibitory correlations of this kind arise naturally in recurrent circuits. Together these two papers should provide additional motivation for those mapping the fine-scale architecture of cortical microcircuits and for those seeking to determine how network architecture impacts information processing.

A.S. Ecker et al. (2010). Science ***327****, 584–587.*
A. Renart et al. (2010). Science ***327****, 587–590.*

Robert P. Kruger