How the Brain Gets Rhythm

Distinctive neural oscillations may link separate brain regions that are responding to the same object. Researchers are now identifying the sources of these vibrations

The brain, in the current opinion of neuroscientists, is a confederacy of dunces, each of them only bright enough to handle one small part of the problem of cognition. The shape of an apple, for example, is recognized by the neurons in one portion of the visual cortex and its color by another portion. How these widely distributed processing areas get bound together to form the apples of perception is one of the central mysteries of neuroscience. But researchers have now moved several steps closer to understanding a phenomenon that may be at the root of the binding.

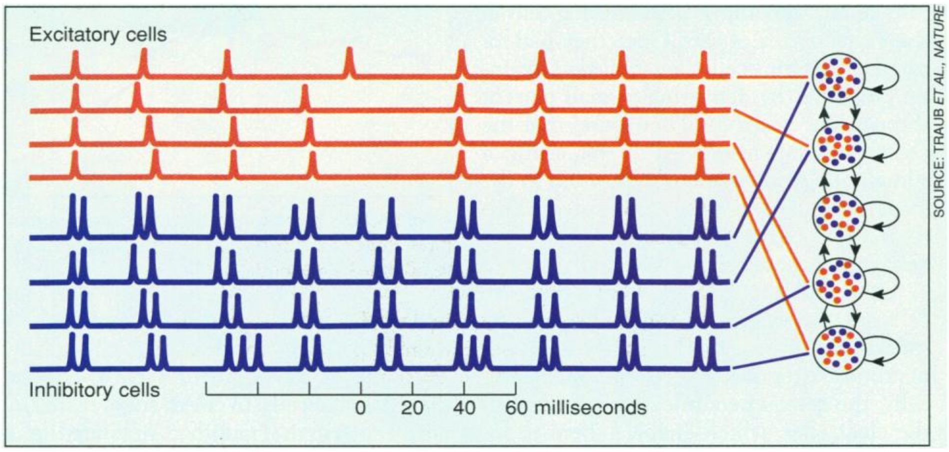
Many researchers believe that the solution to the binding problem lies in regular rhythms in the brain, which seem to become synchronized whenever separate regions are responding to the same apple. But they haven't known where these rhythms come from or how they become synchronized. Two papers, one by Charles Gray of the University of California, Davis, and David McCormick of the Yale University School of Medicine in the 4 October issue of *Science* (p. 109), and the other by Roger Traub at IBM's T. J. Watson Research Center, Miles Whittington of Imperial College, London, and Ian Stanford and John Jefferys of the University of Birmingham in this week's *Nature*, offer the beginnings of an answer.

Or, rather, two complementary answers. By homing in on individual neurons in the living brain, Gray and McCormick have picked out cells that seem to act as excitatory pacemakers for the rhythms. Traub and his colleagues, on the other hand, have looked at groups of neurons in culture and in computer simulations. They conclude that the oscillations emerge as neurons interact in networks, and they think their mechanism can also explain how sets of neurons widely separated in the brain could manage to synchronize their rhythms. But both groups, along with other neuroscientists, believe that these two different mechanisms could coexist in the brain.

"There probably, as usual, will be more than one mechanism," says Wolf Singer of the Max Planck Institute for Brain Research in Frankfurt, Germany, a pioneer in studying these oscillations. And everyone involved is delighted that a 30-year mystery seems to be yielding to experiment. As Traub puts it, "It's the first time you have a mechanism. When you have a mechanism, you can do [further] experiments that get right to the heart of the issue."

Scientists, including Walter Freeman of the University of California, Berkeley, first linked brain rhythms to perception more than 3 decades ago, when they noticed that neurons in the brains of animals tend to fire in rhythmic bursts, 30 to 60 times a second, when they are distinguishing between odors. In the mid-1970s and early 1980s, Peter Milner of McGill University in Montreal and Christoph von der Malsburg of the University of Southern California independently suggested that these so-called gamma oscillations might play a vital role in linking the anatomically distant assemblies of cells that are involved in perceiving a single object. They speculated that these regions get bound together by oscillating in step, but von der Malsburg, at least, was pessimistic that the rhythms could be detected amid the din of other brain activity. "There would be no way to pick them out," he once remarked; "the mind would be invisible."

In less than a decade, that pessimism proved unfounded. In a stunning series of experiments in 1989, Gray, Singer, and their colleagues Peter König and Andreas Engel found evidence for synchronized oscillations in a region known as the primary visual cortex in the brains of cats. The primary visual cortex is organized into columns of cells that respond separately to different aspects of perceived objects: Some fire in response to vertical edges, for example, some to horizontal. Gray and his colleagues showed a cat an image of a moving bar and found that cells responding to the bar, even those separated by an anatomically astronomical distance of 7 millimeters, oscillated in near-perfect lockstep at 30 to 60 hertz. When the experimenters removed the center of the bar and moved both ends, making two distinct objects, the cells still fired, but the synchronization disappeared. The phenomenon that von der Malsburg despaired of glimpsing was becoming visible.



All together now. In a computer simulation, separate clusters of neurons synchronize their firing when inhibitory cells within the groups generate double peaks.

Chattering cells

"The implication of [these] results," says IBM's Traub, "is that the binding problem ... might be experimentally tractable." Gray and McCormick showed as much 2 weeks ago in their *Science* paper. While collaborating with Singer, Gray had discovered that certain cells behave in a surprising way when a cat is given a visual stimulus. Brain researchers often run the output of their probes into loudspeakers to avoid having to look at screens while doing delicate manipulations. These cells, says Gray, "sound a lot like a helicopter—cha, cha, cha—real fast." Gray and McCormick call them chattering cells.

When looked at closely, the chattering cells proved to be firing extremely rapid bursts of action potentials in the familiar gamma frequency range. The spikes within the bursts came as fast as 800 times a second. This chattering, Gray and his colleagues thought, might be the pacemaker for the widespread gamma oscillation, because it is known that rapid bursts of action potentials are far more likely to cause other neurons to fire than are single pulses.

If the chattering cells are in fact the

source of the oscillations, the gamma frequency chatter should be an intrinsic property of these cells and not a response to other oscillating neurons. To find out, in 1992 Gray and McCormick embarked on a series of demanding experiments in cats. Experimenters studying the cat visual cortex usually record the activity of particular neurons through very fine wire electrodes placed near but not in the neurons. But to learn whether a specific cell is setting up a particular rhythm, researchers must be able to stimulate it directly and record its tiny, subthreshold electrical potentials. And that requires monitoring the neuron via an extremely thin, electrolyte-filled tube that pierces the cell membrane. Because the smallest motion of the electrode kills the cell, such experiments are usually performed in vitro on slices of tissues.

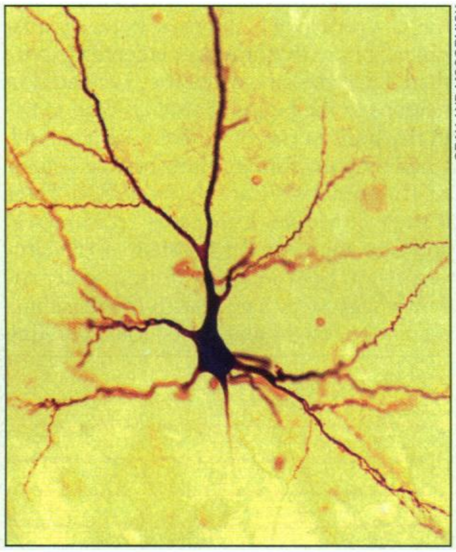
But in what Traub calls "a technical tour de force," Gray and McCormick performed intracellular recordings of chattering cells in the visual cortex of cats. Once they had located a chattering cell, they studied its intrinsic properties by delivering a small current through the electrode. They found that the chattering cells responded to this artificial stimulation in the same way they did to the visual stimulation—they chattered. This rhythmic bursting seems to be an intrinsic behavior of these cells.

Gray and McCormick found that the cells are also well positioned, anatomically speaking, to propagate this rhythm to other neurons. After identifying the chattering cells, the researchers injected dye through the electrodes, which enabled them to locate the cells in brain slices. They found that the chattering cells are a subpopulation of the excitatory pyramidal cells that are common in the outer layers of the cortex. These neurons are known to make widespread connections with other cells, both nearby and farther away in the cortex. "That's very interesting because now you have a cell type that contacts other cortical neurons to excite them to fire in the same rhythm," says Gray. "It doesn't mean we know what the mechanism is, but it gives us a very strong clue."

Network news

Traub and his colleagues have come up with a different set of clues by studying neurons—both real and simulated ones—en masse. Last year, Traub, one of the pioneers in modeling neurons and networks of neurons on computers, produced a model consisting entirely of interneurons—neurons that inhibit the firing of other neurons. He simulated networks of interconnected interneurons on a supercomputer and found that this computerized network responded to a stimulus by vibrating at 40 hertz—a rate determined by how long it takes currents flowing between interneurons to decay, just as the oscillation rate of a spring depends on its stiffness.

At the same time, working independently, Birmingham's Jefferys and Imperial College's Whittington were investigating gamma oscillations in slices of rat hippocampus and neocortex, tissues consisting of inhibitory interneurons and excitatory pyra-



GRAY AND MCCORMICK

Pacemaker. A chattering cell, which stimulates other cells in the cortex by firing rapid bursts 30 to 60 times a second.

midal cells. Whittington and Jefferys bathed their brain slices in drugs that chemically disconnected the interneuron network from the pyramidal cells. In effect, they created in vitro the system Traub had simulated in a supercomputer.

Their interneuron networks, like Traub's, displayed gamma oscillations. "The model was done around the time of the experiment," Traub recalls. "It was really independent. I went to London with my data, and they had their data. It was very exciting. We were looking at the same phenomena. It took a lot of work to show that, but we could see it." What they had glimpsed was a physiologically plausible mechanism that "entrains" other neurons linked to the inhibitory cells to oscillate at 40 hertz.

Now the same group, along with Stanford, has taken on the next question: how different groups of oscillating neurons fall into step across large distances. Neural impulses travel at up to 1 millimeter per millisecond, so two brain regions separated by 10 millimeters are 10 milliseconds apart. But when they are responding to the same stimulus, their oscillations are no more than a millisecond or two out of phase, on the average. Traub hoped that this synchronization might naturally emerge when he added excitatory pyramidal cells to his computer model.

When he modeled neuron clusters containing both excitatory and inhibitory cells, he discovered that the pyramidal cells fired at the gamma rhythm, gated by the rhythmic activity of the network of inhibitory interneurons. Furthermore, instead of firing single spikes, the interneurons fired two rapid spikes, which Traub calls doublets. The lug between the spikes in a doublet was approximately the time it took a nerve impulse to travel from one group of neurons to the next, which was just what was needed to keep the two groups in step. What determines the spacing of the doublet, in turn, is the time it takes inhibitory and excitatory signals to flow between the neuron groups.

Again, Jefferys, Whittington, and Stanford found evidence that neurons in vitro behave just as predicted by Traub's computer model: When the oscillations in their brain slices were synchronized over long distances, the interneurons fired doublets. At other times, they fired the usual single spikes. "The simulations provide one plausible mechanism through which synchrony can be obtained over large distances," says Singer. Adds Charles Stevens of the Salk Institute, "It's a good result, in a very important topic."

In nature, says Singer, both this network mechanism and the chattering cells that Gray and McCormick have studied could be contributing to the gamma oscillations, with the chattering cells helping set the pace and the network of neurons propagating it. "Usually in neural nets engaged in oscillations, one has cells that suggest a frequency range and network properties tuned to these pacemaker rhythms that enhance and spread the rhythm," says Singer.

But even as researchers close in on the origin of the gamma oscillations, they say they are far from knowing whether these rhythms really do play a role in perception, let alone consciousness, as Nobel laureate Francis Crick has suggested. "There's a lot of activity going on in the brain," says Gray. "It could be that this activity is completely unrelated to consciousness. ... It could easily be that what we're measuring is just the sound of the engine running."

–Bruce Schechter

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Additional Reading

C. M. Gray, A. K. Engel, P. König, W. Singer, "Oscillatory responses in cat visual cortex exhibit inter-columnar synchronization which reflects global stimulus properties," *Nature* **338**, 334 (1989).

M. A. Whittington, R. D. Traub, J. G. R. Jefferys, "Synchronized oscillations in interneuron networks driven by metabotropic glutamate receptor activation," *Nature* **373**, 612 (1995).