Listening In on the Brain

Armed with many electrodes at once, neurophysiologists are uncovering synchrony in neural firing that may represent a new way of encoding information

If you try to record a symphony using a single microphone that can pick up only the notes played by one musician at a time, you are likely to get an extremely limited impression of the music. Your recording will miss virtually all the symphony's melodic and rhythmic form. That's the position some neurophysiologists say they find themselves in when they try to understand how the brain works using traditional methods of recording brain activity one neuron at a time.

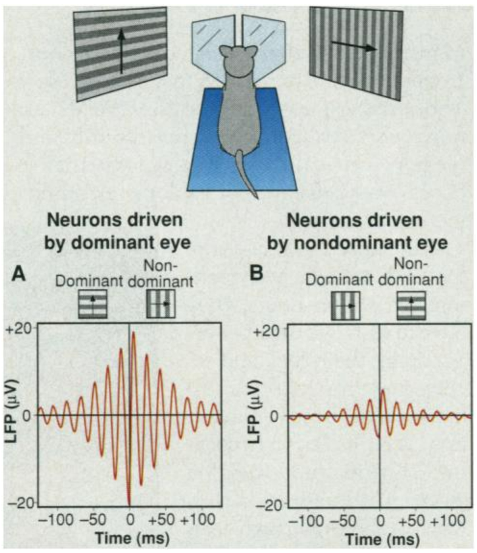
Those techniques have provided—and still are providing—a wealth of knowledge about how brain neurons encode information by varying their firing rates. But as long as 3 decades ago, some neuroscientists, eager to see what they were missing, started recording from multiple electrodes at once. After a slow start, that approach is finally coming of age. Recent results gleaned from such experiments suggest that the brain encodes information, not just in the firing rates of individual neurons, but also in the patterns in which groups of neurons work together.

One of the more tantalizing—and controversial—of these discoveries is that neurons frequently fall into step with one another, forming ensembles that play the same tune, as it were, firing in relative synchrony for brief periods, before some neurons drop out of synch, perhaps to join another ensemble. What's more, studies of systems as diverse as the motor cortex of monkeys and the olfactory system of honeybees indicate that these changing patterns of synchrony correlate with specific behaviors such as a monkey's preparation to move its hand or a honeybee's discrimination of odors.

These findings suggest that the patterns contain information, a situation that if true "would be quite remarkable," says Eberhard Fetz, a neurobiologist at the University of Washington, Seattle, because it would "dramatically increase" the brain's information-encoding capacity. But, adds Fetz, who studies synchronous neural activity in monkeys, "a lot of people think there is no need for [a synchrony code], because the firing rates themselves provide enough [information-encoding] possibilities." Indeed, the case for a role for synchrony is far from proven, says neuroscientist Ad Aertsen, of Albert Ludwigs University in Freiburg, Germany, who designs methods for analyzing data from multiple-electrode recordings. "There is still a lot of need for ... efforts to relate [the patterns] to behavior and see what kind of information they might contain."

Tuning in to the ensembles

Single-electrode experiments have been so successful that neuroscientists have had little incentive to take on the technically challenging task of recording from many neurons at once, says neuroscientist Moshe Abeles, of Hadassah Medical School in Jerusalem: "Most researchers felt they could get a lot of exciting results with a single electrode." Nevertheless, a handful of laboratories, led by George Gerstein at the University of Pennsylvania—who began his multi-electrode experiments in the 1960s—have risen to the challenge. The small field moved slowly at first, as researchers solved technical problems and developed ways to handle the data. But by the 1980s, these pioneers established that neurons often fire together for brief periods—their action potentials mirroring each other to within a few milliseconds.



ADAPTED FROM FIG. 4 IN FRIES ET AL., PROC. NATL. ACAD. SCI. USA 94, 12699–12704

To see or not to see. Brain neurons that respond to the image that a cat perceives (A) show a high degree of synchronous firing (represented by the amplitude of the waves); less synchrony is shown by neurons responding to the eye whose image is not perceived (B).

That synchronous firing suggested that neurons can form a functional group, or ensemble, says Gerstein. And those ensembles are not fixed. "In behaving [animals] or situations where you vary the stimulus, these synchronizations occur dynamically," he says. "Assemblies come and go." That fluid response to changing situations "was really a surprise," adds Abeles. It suggested that the changing patterns may encode information.

But if they did encode information, what was its function? A clue came in the late 1980s from work by neurobiologist Wolf Singer and his colleagues at the Max Planck Institute for Brain Research in Frankfurt, Germany. Singer's team showed that neurons in the visual cortex of cats that respond to different images on a screen, such as two bars, would fire together when the bars moved with the same speed and direction, as if they were part of the same object. But when the bars appeared to be parts of different objects, the neurons fired at the same rates as before but not in synchrony.

Those findings piqued neuroscientists' interest because they suggested that synchronous firing may help solve the "binding problem"—the brain's need to somehow link neural signals that are related to each other, such as all the cues from neurons responding to different visual aspects of an object (*Science*, 24 August 1990, p. 856).

More recent experiments by the Singer team suggest that synchrony may determine not only how the brain perceives stimuli—for example, as parts of the same object—but even whether it perceives them at all. This conclusion comes from studies on strabismic cats, whose eyes are misaligned like those of a cross-eyed person, so that each eye looks at a different part of the surrounding world. The cats don't perceive both conflicting images at once; the brain ignores the image from one eye or the other, so the cat only perceives the image from one eye at a time.

The researchers used mirrors to reflect a different moving image on a screen to each of a cat's eyes, and they monitored the cat's eye movements to determine which image it perceived. When only one eye was presented with an image, that is what the brain perceived. But the researchers could snatch perception from that eye by presenting a rival image to the other eye. By altering the comparative contrast of the images, Singer's team found conditions under which a particular image always won. Then they used electrodes to record the activity of neurons in the cats' visual cortex that respond to signals from the eye watching the original image, while using the rival image to control which eye would win the battle for perception.

When they looked at just the firing rates of the neurons, they could get no clue about whether the image was being perceived by the brain, Singer says. The neurons' firing rates didn't change at all when perception was shifted away. But, he adds, "there was a very clear predictor of perception, and this was the change in synchronicity. When it went up, we knew this eye was the winner; when it went down, we knew this eye was the loser." That, says Singer, suggested that synchronous firing "selectively raises the saliency" of the signal and "predisposes that activity for further joint processing" by higher areas of the visual system. The experiment is intriguing because it provides "an example where synchrony does something that firing rates don't," says Fetz.

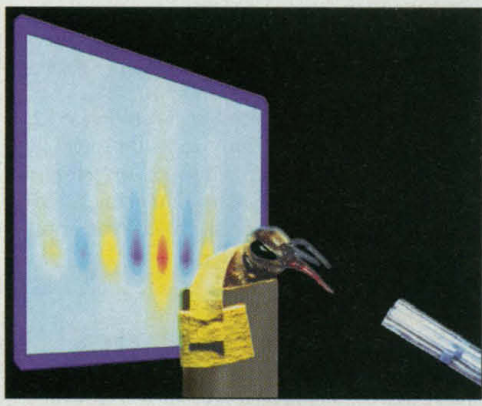
Choreographing a move

Researchers studying other brain regions are finding apparent uses for synchrony as well. In the motor cortex, where neurons fire to direct movements, researchers have found patterns of synchronous activity that seem to help prepare for a move. In one example, Alexa Riehle of the CNRS Center for Research in Cognitive Neuroscience in Marseille, France, in collaboration with Aertsen, trained monkeys to watch a computer screen for a cue, and then, when they received a go command, to touch the screen where the cue had appeared. In each trial, the go command came either 600, 900, 1200, or 1500 milliseconds after the place cue, an arrangement the team chose so that the animals would learn to anticipate when to expect the go signal. They wanted to see how that anticipation—"a pure cognitive signal," as Riehle calls it, with no input from the outside world—would be represented in neural activity.

The researchers simultaneously recorded the activity from up to seven neurons in each monkey's motor cortex while it performed the task. The neuronal firing rates jumped when the go signal told the monkey to touch the screen. That was expected, as activity in the motor cortex controls movement.

But more interesting, Riehle says, were the patterns with which the neurons fired relative to each other during the waiting period, when the animals anticipated a go signal that didn't come. Although the neurons didn't change their firing rates at the moments of anticipation, says Riehle, "we detected a significantly higher amount of synchronization than expected by chance" surrounding those moments. The synchrony formed a changing and predictable pattern. Among the seven neurons she studied in any trial, neuron number 1, say, might briefly fire in synchrony with neuron 3, then fall out of step with 3 and join in with neuron 5.

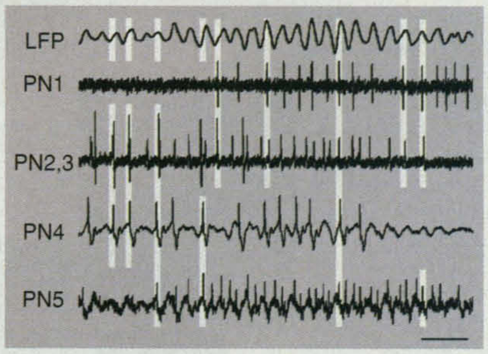
What's more, the synchrony was most intense in those trials in which the monkeys showed the shortest reaction times upon receiving the true go signal, suggesting that the monkeys were highly motivated and attentive. "We think of it [the synchrony] as ... the pretuning and preshaping of the networks that will be involved ... in the execution of the movement," says Riehle. As in Singer's experiments, the synchrony seems to be performing a binding function, in this case linking together the neurons that will need to act together to execute the movement.



MARK STOPPFER AND GILLES LAURENT

Recent experiments by John Donoghue and his colleagues at Brown University in Providence, Rhode Island, suggest that synchrony is involved not only in binding together neurons during movement planning but also in encoding information for actually making the movements. Donoghue's team trained monkeys to use a mechanical drawing arm to move a cursor on a computer screen to the location where a cue appeared.

When Donoghue's group recorded from up to 21 neurons at once in a monkey's motor cortex while it did the task, they found that, on average, 30% of the neurons fired in synchrony at any one time. A mathematical analysis also showed that the synchrony patterns could predict the direction of the monkey's arm movements. "We know [the synchrony pattern] is carrying information about direction," says Donoghue. "But we don't know whether that information is available to the brain to be used for anything. All we know is it is there."



MICHAEL WEHR AND G. LAURENT

Smells good. Firing patterns of individual neurons in the antennal lobe of a locust show transient pairwise synchrony (open boxes) in response to an odor. Such patterns help a honeybee, shown at top with extended proboscis, recognize an odor.

The signature of a sniff

One case in which the brain definitely seems to be using the information encoded in synchronous firing is in the olfactory system of insects. Gilles Laurent at the California Institute of Technology in Pasadena and his colleagues study the part of an insect's brain called the antennal lobe, where the neurons process smells. In locusts, the lobe has about 1000 neurons, and about 100 of them fire action potentials in response to any odor. Not only is information contained in the pattern of activated neurons, Laurent says, but there is also information in the neurons' timing with respect to one another. "It is very clear that the temporal patterns are stimulus specific," he says. "Knowing the precise timing of the spike gives you additional information about the odor."

As in Donoghue's case, the existence of that information doesn't necessarily mean the brain uses it. However, Laurent's team was in a position to address that question directly. That's because his group had discovered that a neurotoxin called picrotoxin abolishes the synchronous firing of neurons in the antennal lobe in response to odors, without altering their firing rates. Armed with the ability specifically to get rid of the synchrony, Laurent's team was ready to ask whether synchrony is essential to an insect's ability to distinguish among odors.

To do that experiment, his team used honeybees, which can be trained to recognize odors associated with a sugar-water reward. Working with Brian Smith at Ohio State University, the researchers trained picrotoxin-treated and control bees to associate an odor with a reward. Bees show they have learned an odor by sticking out their tongues in expectation of the reward. Both groups of bees did equally well.

But a difference between the groups emerged when the researchers tested whether the bees could discriminate the familiar odor from other odors. Both groups could do this just fine when the familiar odors were very different from one another. But when the odors were very similar, the picrotoxin group failed. That led Laurent to conclude that the timing of the spikes in relation to each other is important for fine discrimination of odors. The Laurent team's study, says Aertsen, "really addresses the issue: Can you show that if the synchrony isn't there, the system doesn't work."

But although "the olfactory system is certainly a specific place where cofiring of neurons means a lot," says Hadassah's Abeles, he would like to see more evidence in other systems that the brain is really using the information encoded in the synchrony. Singer argues that his binocular rivalry experiments make a good case that it is. "Since it is such a strong predictor of perception, I can't imagine that the brain ignores synchrony," he says. "It is inconceivable. It would be like saying that the brain ignores firing rate."

Despite arguments such as Singer's, some researchers remain skeptical about the function of synchronous firing in the brain. It may just be a product of neurons changing their firing rates at the same time, argues neuroscientist Michael Shadlen of the University of Washington. Like a group of people who all start to run at once, their first few steps may be nearly in unison.

Researchers who study synchrony often find no change in the firing rates of neurons when they synchronize, but Shadlen notes that changes in firing rate can only be seen when they are time locked to something the researcher controls, such as the appearance of a cue on a computer screen. That's because the only way to measure firing-rate changes accurately is by averaging the response of neurons over many trials. If the neurons are changing their rate in response to something the experimenter doesn't control, such as when a monkey happens to make up its mind, says Shadlen, that event may change with each trial, and consequently the rate change may be invisible to the experimenter.

In that case, says Shadlen, studying synchrony would still be important, because it can reveal mental events researchers otherwise would have no way of detecting. "I'm saying synchrony lets us find the rate changes, and they are saying synchrony is the code," says Shadlen. Regardless of who is right, the study of the synchronous firing of neurons is sure to help researchers record the music of the brain for years to come.

–**Marcia Barinaga**

Additional Reading

P. Fries *et al.*, "Synchronization of oscillatory responses in visual cortex correlates with perceptin in interocular rivalry," *Proceedings of the National Academy of Sciences* **94**, 12699 (1997).

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M. N. Shadlen and W. T. Newsome, "Noise, neural codes and cortical organization," *Current Opinion in Neurobiology* **4**, 569 (1994).

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INFRARED ASTRONOMY

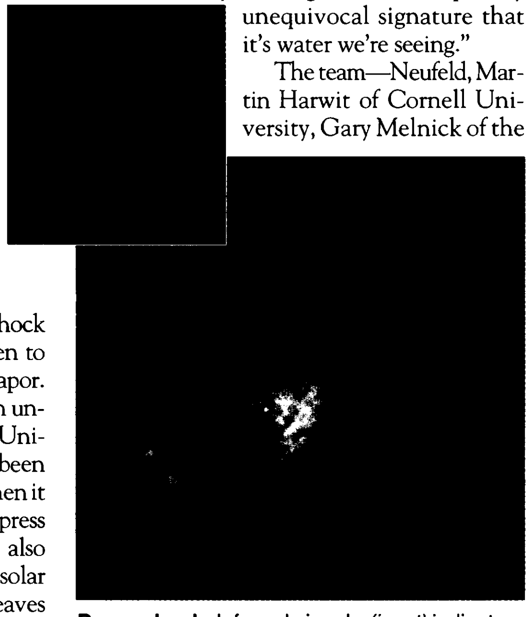
A Water Generator in the Orion Nebula

The discovery is too distant for seaside vacations and too tenuous to be considered a natural resource. But when, like an orbiting dowser, instruments aboard the Infrared Space Observatory (ISO) picked up an intense glow from a cloud near the Orion Nebula, astronomers knew they had found a concentration of water that makes the Pacific Ocean look like a drop in the bucket. The measurement, which will be reported in the 20 April issue of *Astrophysical Journal Letters*, turned up the highest concentration of water ever seen outside the solar system.

The find confirms theories of how shock waves heat such clouds and induce oxygen to combine with hydrogen and form water vapor. "There was no observational confirmation until now," notes Bruce Draine of Princeton University, who says the field would have been "dumbfounded" if ISO had come up dry when it pointed its instruments at Orion. In two press releases, the team suggests that the find also offers clues to how water collected in the solar system and on Earth—a speculation that leaves researchers like Draine feeling skeptical.

Most previous detections of water outside the solar system have relied on naturally occurring masers—the microwave equivalent of lasers. Because even minute amounts of water can give large maser emissions, pinning down the concentrations has proved impossible. Instead, ISO's Long Wavelength Spectrometer captured infrared emissions from water vapor caused by thermal agitation. (The measurements couldn't be made from the ground because of the veil of water in Earth's atmosphere.) "We have eight different wavelengths at which water is emitting," says David Neufeld of The Johns Hopkins University. "That gives us a completely unequivocal signature that it's water we're seeing."

The team—Neufeld, Martin Harwit of Cornell University, Gary Melnick of the Harvard-Smithsonian Center for Astrophysics (CfA), and Michael Kaufman of NASA Ames Research Center—pointed the instruments to an area in the cloud about a third of a light-year across, near which lies a hot, young star in a nursery of stellar formation called Orion BN-KL. Such stars throw off powerful winds and jets, driving shock waves when they collide with surrounding material. According to theory, the shocks heat the gas, speeding up chemical reactions that cause all of the free oxygen to combine with hydrogen atoms—by far the most abundant species—into water.



EUROPEAN SPACE AGENCY / NASA

Damp shock. Infrared signals *(inset)* indicate that shock waves from a young star in Orion are inducing hydrogen and oxygen to combine.

At about 2000 kelvins, the shocked gas seen by ISO is well above the threshold for that process to take place, says Neufeld. The precise levels of water that were measured—about 20 times denser, compared to the hydrogen, than ISO had ever seen before—"are in essentially perfect agreement with theory," he says. "With the radio masers you are seeing little, tiny diamonds" of emission, says James Moran of CfA. "Now it seems that this exists on a scale 100,000 times larger."

"It's an exciting discovery," agrees CfA's Alex Dalgarno, the editor of *Astrophysical Journal Letters*. But even though Neufeld calculates that the shocks in the cloud are creating water at a rate fast enough to fill Earth's oceans 60 times a day, Draine and Dalgarno cast doubt on the more speculative idea that water from such a cloud might find its way into a forming planetary system. "This at least raises the possibility, [but] how would the water survive the formation of the solar system?" asks Dalgarno.

Shocks within the forming system are a more likely candidate, says Draine. Neufeld agrees that the hypothesis of shocks as the source of our water should be considered "just as a general notion" and not solely as a way of sprinkling the solar system with primordial water. But for observers who have been thirsty for a good look at water in space, that could be enough to tell them the surf's up.

–**James Glanz**