# CHIPS ON THE OLD BLOCK

## Microelectronic chips serve as newfangled tools for eavesdropping on brain chatter

By JULIE ANN MILLER

Enjoying a pleasant memory, working out a math problem, jumping out of the way of a speeding bicycle — all these activities depend on interactions among billions of brain cells.

Biologists have made impressive progress in determining the basic elements of these interactions. They have described the types of cells and mapped their connections. They have determined precisely the chemical and electrical bases for the interactions. It is as if in observing a convention, one had determined who was attending and what languages they were speaking. The next step would be to learn what the delegates were actually saying to each other.

Analysis of conversations among groups of nerve cells is the next critical step in learning how the brain processes information. But the abundance of brain cells, and a lack of appropriate tools, has made it a difficult challenge. Microelectrodes, the fine metal needles or glass tubes that are used to record signals in the brain, generally give information about the activity of only one cell at a time. Other current techniques, such as positron emission tomography (PETT), reveal the overall activity of large areas of the brain.

Recently, interest has focused on interactions within groups of nerve cells. Scientists speculate that the complexity of brain operation may be simplified by identifying fundamental components or "modules," groups of hundreds to thousands of nerve cells interacting in a characteristic pattern. Convention-goers, in the analogy, may participate in different workshops, each having approximately the same format; committee caucuses, with another format; or informal discussion over coffee. The outcome of each "module" influences the outcome of the convention.

By listening only to the utterances of a single delegate, it would be difficult to determine what type of meeting was under way and how the opinions expressed would influence any overall decision. But by analyzing the speech of a variety of delegates simultaneously over the course of the convention, one might determine how various actions influenced others as policy was being made.

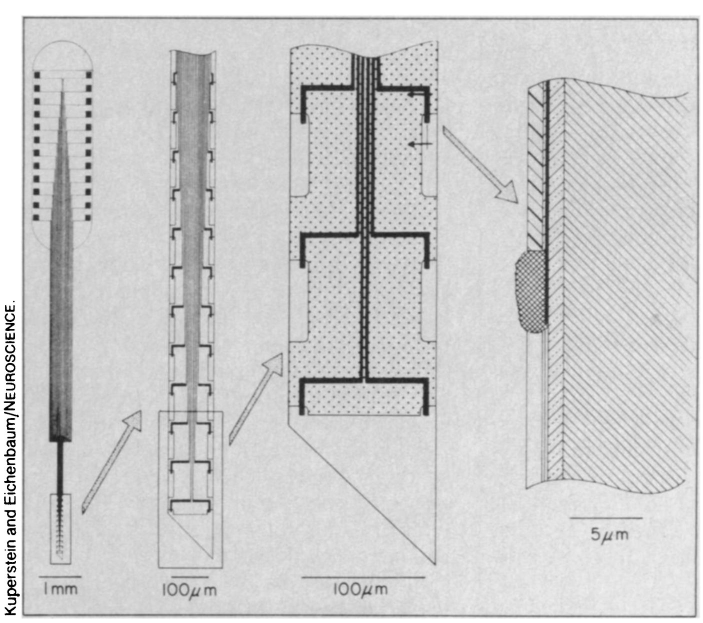
New electronic techniques are being developed to eavesdrop on the brain by detecting the activity of many cells simultaneously. The techniques employ integrated circuit chips that can be either implanted in the brain or overlaid with brain cells. Such chips, containing complex circuits built into the surface of silicon wafers, can record signals simultaneously from many nerve cells.

One such tool already in use to eavesdrop on the intact brain is called PRONG, for Parallel Recording of Neural Groups. Developed by Michael Kuperstein and Howard Eichenbaum of Wellesley (Mass.) College, this electrode can measure up to 24 individual signals, spaced as little as 100 microseconds apart, from neighboring nerve cells as close as 20 microns apart. Standard microelectrodes are limited to a spatial resolution of about 1 centimeter, Kuperstein says.

The PRONG electrode consists of an array of 24 gold leads sandwiched between layers of insulator on a thin molybdenum foil. At the recording sites, a blob of platinum black carries current through a hole in the insulation. The recording area of the electrode is 0.1 millimeter wide and 1.3 millimeters long. The electrode is connected to a 24-channel preamplifier, amplifier, monitor, high-speed digital and analog interfaces and finally a computer. The electrode can be connected to an animal's skull for repeated observations of electrical activity over several days.

In a recent experiment, for example, the Wellesley scientists inserted the PRONG electrode into the brain of an anesthetized rat. They were able to record simultaneously from 19 different cells in the brain area that receives olfactory information. The electrical signals they detected were "essentially identical" to recordings using conventional electrodes, they report. "No one has gotten so many simultaneous recordings," Kuperstein says.

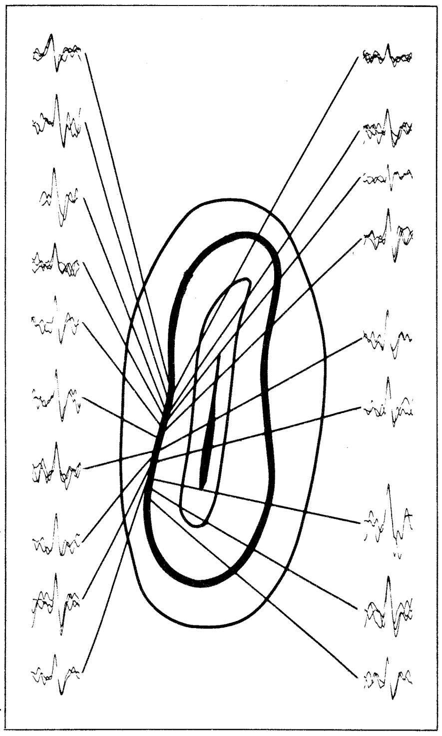
Kuperstein and his colleagues have used their microelectrodes to detect patterns of cellular activity in the part of the brain called the hippocampus, which plays a role in storing memories and generating emotions. For more than a decade, different states of hippocampus ac-




Kuperstein and Eichenbaum/NEUROSCIENCE.

*The PRONG electrode has 24 recording sites that connect through contact pads at the top to a 24-channel preamplifier. The conducting material is shown in solid black. The cross-section shows the platinum black, cross-hatched area that carries current from the brain into the electrode.*

tivity have been crudely detected from outside the skull by electroencephalograms (EEGs). One pattern, called the theta rhythm, predominates in rats during REM sleep and exploring behavior. Kuperstein recently reported in EXPERIMENTAL BRAIN SCIENCE (Vol. 61, p. 438-442, 1986) that correlations of the activities of 4 to 14 cells in each of 22 recording sessions revealed a rhythmic synchronization of cell activity during the theta state, distinct from other states. "The combined findings suggest that the theta rhythm signifies a powerful patterning of group activity imposed upon a fixed connectivity of neighboring neurons," the scientists conclude.



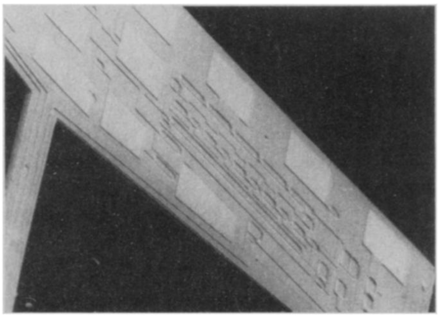
Kuperstein and Eichenbaum/NEUROSCIENCE.

*The PRONG electrode has recorded electrical signals simultaneously from 19 sites in this brain area, which processes olfactory information.*

The same goal, simultaneous electrical recording from brain cells, is being approached by a slightly different path at the University of Michigan at Ann Arbor. Ken Wise and his colleagues are fabricating an electrode with 12 recording sites and, in addition, an array of electronics to amplify the signals detected and combine the signals for transmission from the probe over a single thin wire. They predict that by not requiring a separate wire for each recording site, they will reduce the number of short circuits and pose less risk of infection.

Wise and colleagues David J. Anderson and Spencer Bement have tested in gerbil brains a prototype probe that lacks the amplifiers. "It can record separate neural activity in individual sites on the electrode over extended periods of time — several hours," Anderson says.

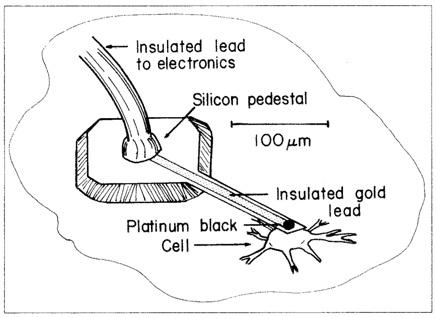
A different approach to the nerve cell-silicon connection is under way in other laboratories. By working with nerve cells removed from the brain and grown in special laboratory solutions, the scientists have a better chance to sense what goes on inside cells.



Wise, Univ. of Michigan

*The signal-processing circuits on the top of a 3-electrode microprobe.*

Using techniques developed for the fabrication of computer chips, Jerome Pine, David Rutledge and Wade Regehr of the California Institute of Technology in Pasedena are devising a "diving board electrode" for intracellular recordings. They plan to make an electrode that will extend from a silicon pedestal to contact a nerve cell growing on a laboratory plate. The electrode, made of gold, is insulated except for a spot 5 microns in diameter that will be covered with platinum black. The scientists plan to use a brief burst of high-voltage current to blast a hole in the cell's membrane. Then they predict that the cell membrane will seal around the electrode to make a stable connection.




Pine and Rutledge, CalTech

*Plans for the diving board electrode, which is intended to allow long-term recording from nerve cells grown under laboratory conditions.*

To allow simultaneous recordings from several cells, Pine and his colleagues are building "neurochips," which will house on a silicon wafer at least 16 nerve cells in wells with electrodes at their bases. They plan to inject immature nerve cells into the wells and let the cells extend their long fibers — axons and dendrites — to form connections with each other. Then the scientists plan to record communication among the selected nerve cells, and perhaps even put the neurochip into an animal's nervous system so that the "wired" cells establish connections with the intact brain.

Other research teams are also building arrays of electrodes to study cells in laboratory culture. David Tank and his colleagues at AT&T Bell Laboratories in Murray Hill, N.J., have constructed chips containing arrays of 64 electrodes, although so far they have only recorded from two cells simultaneously. They have been focusing on "the physics of the electrical connection," in order to devise the best conditions for making their observations.

The Bell scientists have examined different chip materials that might best support cells of invertebrate animals. They have had their greatest success with silicon nitride, to which the cells stick firmly. They position a gold electrode in a hole through the silicon nitride. When the cell adheres to the substrate over the area surrounding the electrode, the scientists can record large electrical signals, Tank says. Occasionally a large cell covers several electrodes, and in these cases the scientists can record somewhat different signals from different parts of the cell.

Tank and his colleagues have applied a large-voltage pulse to break down partially the cell membrane. While the electrode appears to remain outside the cell, the signals recorded are almost identical to those measured by conventional electrodes inserted into a cell. Pines calls these observations "a new form of electrical connection," in which the membrane becomes highly conductive although it is not completely broken down.

Using a similar technique, other scientists are growing rat embryonic brain cells on computer chips. Martin Peckerar of the Naval Research Laboratories in Washington, D.C., has built a 30-electrode chip that is 3 to 5 microns across. Richard Wyatt of St. Elizabeth's Hospital, also in Washington, has used it to record from up to 30 rat cells for approximately a week. "We now have a chance of figuring out how these cells talk," Wyatt says.

Even more speculative, but tantalizing, is the possibility of using chip electrodes not only to eavesdrop on but also to direct brain cell conversations. "Our distant hope is to develop software to allow us to talk to neurons," Wyatt says. "In the future, we might put a chip in the brain to communicate with brain cells in a semi-intelligent manner."

Such electrodes permanently implanted in the brain might be able to receive and generate electrical signals to bypass damaged nerves and deliver electrical signals to appropriate nerve cells or muscles. Pine also suggests that neurochips may be used to control artificial limbs.

But the work is only in early stages. "It's an art; there's no science yet," Wyatt says. "We haven't published anything on this yet. We just keep struggling." □