

Monkey Feel, Monkey Do

SENSORY PERCEPTION INVOLVES NOT JUST ONE BUT MANY AREAS OF THE BRAIN.

Responding to sensory information may take more than a simple flip of a switch in one area of the brain, according to recent research performed in monkeys. HHMI international research scholar Ranulfo Romo and his colleague Victor de Lafuente have found



Neuroscientists are feeling their way around sensory perception with help from rhesus macaques (*Macaca mulatta*).

that a gradual buildup of information across numerous sections of the brain is needed. The duo's research findings appeared in the August 21, 2006, online version of the *Proceedings of the National Academy of Sciences*.

By attaching electrodes to single neurons in different areas of the brain, specifically the cortical areas of the frontal and parietal lobes, Romo and Lafuente, at the Institute of Cellular Physiology, National Autonomous University of Mexico, arrived at this answer by training a pair of monkeys to report the presence or absence of a vibratory stimulus applied to one of their fingertips. Animals pressed on one of two buttons to indicate whether the stimulus was present or not, and were rewarded with a drop of liquid for correct responses. The researchers found that the train of thought needed to pass through numerous stations as neuronal activity spread from the lower somatosensory cortex of the parietal lobe, which sensed or felt the vibration, to the higher premotor area of the frontal lobe, which sent the signal to push the button.

"The action of these cortical areas gradually predicts whether the monkey is going to detect or not going to detect the stimulus," says Romo, who plans to further confirm his findings by doing simultaneous recordings of multiple neurons in these brain regions.

Figuring out how sensory experiences arise from activity in the brain is a huge challenge in neurophysiology, says Romo, adding that the paper "helps fill in the gaps." ■ - JACQUELINE RUTTIMANN

IN BRIEF

scientists distinguish "driver genes," which are mutated genes that cause cancer, from "bystander" genes, which are mutated but do not cause cancer. They identified two such driver genes, *cIAP1*, which prevents cell death, and *Yap*, which promotes cell proliferation. The new mouse model is also likely to facilitate development and testing of new drugs to target liver cancer.

NEW INSIGHT INTO EGFR ACTIVATION

In a discovery that may help design new cancer drugs, researchers have provided a definitive look at how the catalytic center of the epidermal growth factor receptor (EGFR)—a protein often implicated in cancer development—turns itself on to promote cell growth. The researchers, led by HHMI investigator John Kuriyan at the University of California, Berkeley, published their findings in the June 15, 2006, issue of *Cell*.

In healthy cells, EGFR triggers growth in response to a signal coming from outside the cell. When signaled, EGFR receptors on the cell surface form pairs, causing a physical change in the shape of the catalytic center of the protein, called the tyrosine kinase domain. The normally inactive kinase is activated, sending signals into the cell that trigger cell growth.

Kuriyan and colleagues demonstrated that the kinase domains of EGFRs are normally in the off state but are switched on when placed next to one another. Using x-ray crystallography to determine the kinase domain structure, the researchers found two possible conformations—a symmetric form, in which both units had the same relative position to each other, and an asymmetric form, in which one unit took a different position relative to the other. The asymmetric conformation, they determined, is important for activation.

EGFR is the target of several cancer drugs currently in development, as well as several approved therapies. The researchers say their findings offer clues for the design of next-generation EGFR inhibitors.

A NEW WAY TO BUILD BONE

Stanford University researchers have found that they can increase bone mass in mice by tweaking the shape of a regulatory protein. HHMI investigator Gerald R. Crabtree and HHMI predoctoral fellow Monte Winslow report that a slight bump in the activity of a protein called NFATc1 causes massive bone accumulation, suggesting that NFATc1 or other proteins that regulate its activity will make good targets for drugs to treat

osteoporosis. They report their findings in a study published in the June 6, 2006, issue of *Developmental Cell*.

In vertebrates, bone is constantly being formed and broken down by a balance of two cells: osteoclasts, which continuously degrade bone, and osteoblasts, which replenish it. If the balance is upset and more bone is destroyed than formed, osteoporosis results, increasing the risk of fractures. Patients who were treated with the drug cyclosporine—often given to suppress the immune system before organ transplants—tend to lose bone mass like osteoporosis patients. Cyclosporine inhibits a signaling protein complex known as calcineurin, which chemically modifies and changes the shape of the NFATc family of proteins that then move to the cell nucleus and trigger multiple gene activation.

The researchers found that mice with enhanced NFATc1 activity in their osteoblasts had many more of these bone-forming cells and an increased bone mass. They also found a possible reason for the increase in bone-destroying osteoclasts: The altered osteoblasts expressed higher levels of inflammatory proteins called chemokines, which promote osteoclast development.