



Figuring out the brain functions that underlie human behavior has been a little like trying to understand the interior of a movie projector based on the pictures you see on a screen. Theoretically, with new technologies like functional neuroimaging, scientists can monitor brain activation in both animals and humans engaged in a variety of activities and complex behaviors. Yet such studies often present a challenge, since subjects usually must be immobilized for the imaging equipment to get a clear view of activated brain regions. As a result, evaluations may be limited to just a few simple behaviors.

Labeling Active Brain Regions

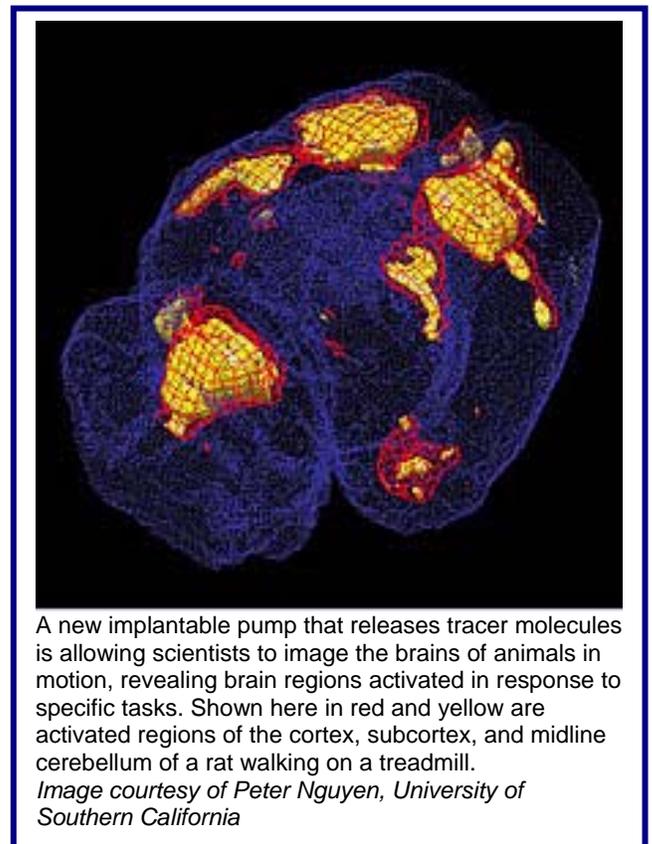
Now scientists led by Dr. Daniel P. Holschneider, an associate professor in the department of psychiatry at the University of Southern California, have engineered a unique device that may significantly enhance functional brain studies in animals. The researchers, funded by NIBIB and the Whitaker Foundation, developed a miniature implantable device – called a microbolus infusion pump – that releases radioactive tracer molecules into the bloodstream by remote control. Just before an animal begins the activity under study (such as running or feeding), scientists activate the pump to release the molecular tracers, which then hitch a ride with blood flowing into the brain. Scientists next use a technique called autoradiography to detect the distribution of tracer molecules, thereby revealing brain regions with greatest blood flow—a sign of brain activation.

The researchers tested the pump by implanting it in rats and placing the animals on a treadmill. Compared to control animals that listened to the sounds of the treadmill but did not exert themselves, rats moving on treadmills had increased brain activation in motor circuits and in cortical regions known to control the forelimbs, hind limbs, and trunk.

Dr. Holschneider and his colleagues are now working to enhance the pump's versatility. They are developing an even smaller pump that can be implanted into mice. The researchers are also exploring how the pump might be used to label activated brain regions prior to noninvasive scans with advanced imaging technologies, like positron emission tomography (PET). Compared to autoradiography, PET can be used repeatedly to study a single animal, allowing that subject to be examined as its own control as well as in several different behavioral situations. In some conventional PET studies of animals in motion, scientists administer radioactively labeled sugar molecules, which are consumed and used as fuel by activated brain cells. But the radiolabeled sugar presents a drawback for functional neuroimaging studies of behavior. The lag time from administration to uptake and capture of the labeled sugar by brain cells is about 25 to 45 minutes, whereas many behaviors, such as aggressive behaviors, are more short-lived.

Improving Tracer Delivery

Dr. Holschneider's current challenge is to apply radioactive tracers that are captured by brain cells in a shorter time frame during brief bursts of activity and yet remain in the brain long enough for the animal to be anesthetized and put into a PET scanner for analysis. The radioactive molecule must also be sufficiently short-lived, so that the signal can clear from the body and the animal can be used later in a control experiment. Dr.



Holschneider has identified several compounds that appear to have those very properties, but more studies are needed to confirm their usefulness.

With these advanced technologies in hand, Dr. Holschneider plans to investigate animal models of human psychiatric disorders. One goal is to study mice that are deficient in the enzyme monoamine oxidase A (MAO-A), a target of some antidepressants. “This enzyme is well-known to play an important role in neurotransmitter metabolism,” he says.

References

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