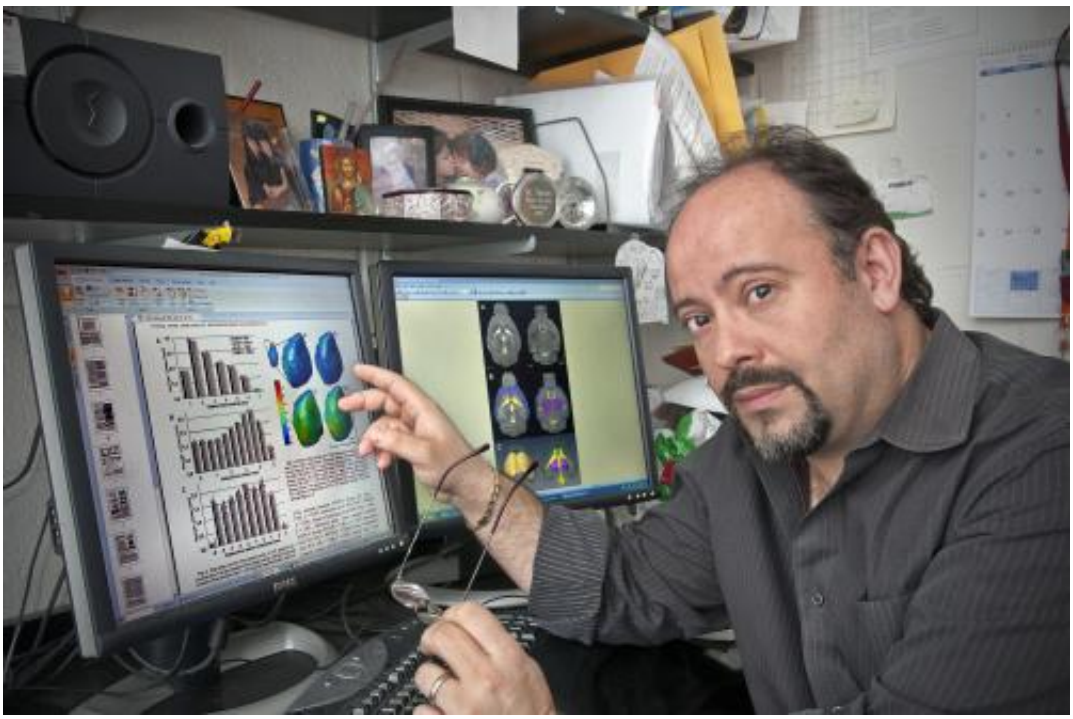
PET scans monitor brain circuits activated by light, opening new window to brain diseases

April 11 2013



Peter Thanos.

(Medical Xpress)—Building on their history of innovative brain-imaging techniques, scientists at the U.S. Department of Energy's Brookhaven National Laboratory and collaborators have developed a new way to use light and chemistry to map brain activity in fully-awake, moving animals. The technique employs light-activated proteins to stimulate

particular brain cells and positron emission tomography (PET) scans to trace the effects of that site-specific stimulation throughout the entire brain. As described in a paper published online today in the *Journal of Neuroscience*, the method will allow researchers to map exactly which downstream neurological pathways are activated or deactivated by stimulation of targeted brain regions, and how that brain activity correlates with particular behaviors and/or disease conditions.

"This technique gives us a new way to look at the function of specific brain cells and map which brain circuits are active in a wide range of neuropsychiatric diseases—from depression to Parkinson's disease, neurodegenerative disorders, and drug addiction—and also to monitor the effects of various treatments," said the paper's lead author, Panayotis (Peter) Thanos, a neuroscientist and director of the Behavioral Neuropharmacology and Neuroimaging Section—part of the National Institute on Alcohol Abuse and Alcoholism (NIAAA) Laboratory of Neuroimaging at Brookhaven Lab—and a professor at Stony Brook University. "Because the animals are awake and able to move during stimulation, we can also directly study how their behavior correlates with brain activity," he said.

The new brain-mapping method combines very recent advances in a field known as "optogenetics"—the use of optics (light activation) and genetics (genetically coded light-sensitive proteins) to control the activity of individual neurons, or nerve cells—and Brookhaven's historical development of radioactively labeled chemical tracers to track biological activity with PET scanners.

The scientists used a modified virus to deliver a light-sensitive protein to particular brain cells in rats. Genetic coding can deliver the protein to specifically targeted brain-cell receptors. Then, after stimulating those proteins with light shone through an optical fiber inserted through a tiny tube called a cannula, they monitored overall brain activity using a

radiotracer known as ^{18}FDG, which serves as a stand-in for glucose, the body's (and brain's) main source of energy.

The unique chemistry of ^{18}FDG causes it to be temporarily "trapped" inside cells that are hungry for glucose—those activated by the brain stimulation—and remain there long enough for the detectors of a PET scanner to pick up the radioactive signal, even after the animals are anesthetized to ensure they stay still for scanning. But because the animals were awake and moving when the tracer was injected and the brain cells were being stimulated, the scans reveal what parts of the brain were activated (or deactivated) under those conditions, giving scientists important information about how those brain circuits function and correlate with the animals' behaviors.

"In this paper, we wanted to stimulate the nucleus accumbens, a key part of the brain involved in reward that is very important to understanding drug addiction," Thanos said. "We wanted to activate the cells in that area and see which brain circuits were activated and deactivated in response."

The scientists used the technique to trace activation and deactivation in number of key pathways, and confirmed their results with other analysis techniques.

The method can reveal even more precise effects.

"If we want to know more about the role played by specific types of receptors—say the dopamine D1 or D2 receptors involved in processing reward—we could tailor the light-sensitive protein probe to specifically stimulate one or the other to tease out those effects," he said.

Another important aspect is that the technique does not require the scientists to identify in advance the regions of the brain they want to

investigate, but instead provides candidate brain regions involved anywhere in the brain – even regions not well understood.

"We look at the whole brain," Thanos said. "We take the PET images and co-register them with anatomical maps produced with magnetic resonance imaging (MRI), and use statistical techniques to do comparisons voxel by voxel. That allows us to identify which areas are more or less activated under the conditions we are exploring without any prior bias about what regions should be showing effects."

After they see a statistically significant effect, they use the MRI maps to identify the locations of those particular voxels to see what brain regions they are in.

"This opens it up to seeing an effect in any region in the brain—even parts where you would not expect or think to look—which could be a key to new discoveries," he said.

More information: Paper: "Mapping Brain Metabolic Connectivity in Awake Rats with μPET and Optogenetic Stimulation"

Provided by Brookhaven National Laboratory