Common algae helps illustrate mammalian brain electrical circuitry

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Mice whose brain cells respond to a flash of light are providing insight into the complexities of the sense of smell and may ultimately yield a better understanding of how the human brain works.

Investigators at Duke University Medical Center and the Howard Hughes Medical Institute have engineered a strain of mice whose olfactory brain cells "fire" when exposed to light. This was accomplished by inserting into the cells a gene naturally present in green algae that "turns on" when exposed to light and enables the algae to swim toward the light.

When the researchers shined light on the areas of the brain involved in smell, they could follow in real time what areas of the brain were reacting and where the signals went by seeing differences in electrical current that indicated the presence of the algae gene.

"This work provides a new method in live animals that will define the experimental approach for studying of mammalian neural circuitry in the coming decade," said Michael Ehlers, M.D., Ph.D., a Duke neurobiologist and Howard Hughes Medical Institute investigator.

The researchers published their findings in the April 19, 2007, issue of the journal *Neuron*. The research was supported by the National Institutes of Health and the Howard Hughes Medical Institute.

"This mouse model and its future variants mark the first use of genetically produced light activation in the study of the intact

mammalian brain, and we believe this advance in nerve circuit mapping will be to neurobiology what microarray technology has been to genomic science -- a fundamental breakthrough," Ehlers said. Microarray technology enables scientists to screen thousands of genes at once to look for clusters of genes that may be involved in disease.

Although there are many approaches to studying how different nerve cells in the brain react to stimuli from the environment, this mouse model is the first to be able to provide real-time mapping of brain circuitry in a living, intact mammal, the researchers said.

The light-producing gene inserted into the mice is taken from the water-dwelling microorganism Chlamydomonas reinhardtii, which, as a plant, needs sunlight for photosynthesis. Tiny hairlike structures along the outside of the algae propel it toward the light. These structures are controlled by channelrhodopsin-2, a so-called "ion channel," which reacts to light by stimulating movement toward it.

While researchers previously have used channelrhodopsin-2 in a variety of experiments in cell culture, the Duke experiments mark the first time the gene controlling its action has been inserted into the genetic makeup of a living mammal, the researchers said. The mice were created by Ehlers' colleague Guoping Feng, Ph.D., assistant professor of neurobiology.

The researchers decided to test the mice first on the sense of smell, since the olfactory system not only involves complex neural circuits but also has a behavioral component.

"The perception of smell is quite complex," Ehlers said. "The brain can decode thousands of smells that enter the nose, discriminating even the slightest scent and often conjuring up vivid memories. So we wanted to know how the brain decodes the presence of these chemicals in the air

and turn them into a perception. It's still quite mysterious."

Ehlers said that even though these experiments shed new light on the inner workings of the olfactory system, their greatest significance is that they provided proof of principle that this new model can be used to study a wide variety of questions involving the brain.

"There are a lot of tools that work well in simpler systems or in isolated nerve cells, but the findings are often difficult to translate into an intact mammalian brain," Ehlers said. "This new model opens up whole new avenues for study. We may reach a future where brain injuries, spinal cord damage, neuron loss in Alzheimer's disease, or even depression are treated by fiber optics delivering light to genetically defined populations of nerve cells.

Source: Duke University Medical Center