Imaging neural progenitor cells in the living human brain

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For the first time, investigators have identified a way to detect neural progenitor cells (NPCs), which can develop into neurons and other nervous system cells, in the living human brain using a type of imaging called magnetic resonance spectroscopy (MRS). The finding, supported by the National Institutes of Health (NIH), may lead to improved diagnosis and treatment for depression, Parkinson's disease, brain tumors, and a host of other disorders.

Research has shown that, in select brain regions, NPCs persist into adulthood and may give rise to new neurons. Studies have suggested that the development of new neurons from NPCs, called neurogenesis, is disrupted in disorders ranging from depression and schizophrenia to Parkinson's disease, epilepsy, and cancer. Until now, however, there has been no way to monitor neurogenesis in the living human brain.

"The recent finding that neural progenitor cells exist in adult human brain has opened a whole new field in neuroscience. The ability to track these cells in living people would be a major breakthrough in understanding brain development in children and continued maturation of the adult brain. It could also be a very useful tool for research aimed at influencing NPCs to restore or maintain brain health," says Walter J. Koroshetz, M.D., deputy director of the NIH's National Institute of Neurological Disorders and Stroke (NINDS), which helped fund the work. The study was also funded by the NIH's National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK).

"This is the first noninvasive approach to identify neural progenitor cells in the human brain," says Grigori Enikolopov, Ph.D., of Cold Spring Harbor Laboratory in New York, who conducted the new study along with co-corresponding author Mirjana Maletic-Savatic, M.D., Ph.D., of the State University of New York, Stony Brook and their colleagues at SUNY Stony Brook and Brookhaven National Laboratory. MRS is an imaging technique that can be used to detect proteins and other compounds normally present in body fluids or tissues. The study results are published in the November 9, 2007, issue of *Science*.

Previously developed techniques using positron emission tomography and other types of brain imaging allow investigators to identify NPCs in animals. However, those techniques require pre-labeling the cells with radioactive agents or magnetic nanoparticles – strategies that are not practical in people. In the new study, the researchers identified an innate property of NPCs that can be detected by MRS. This enables them to image NPCs without introducing drugs or other agents.

The researchers used a technique related to MRS to compare the signals of NPCs from embryonic mice to those of neurons, astrocytes, and oligodendrocytes. Astrocytes and oligodendrocytes are non-neuronal cells that are very common in the brain. The investigators found that NPCs showed a specific signal, or marker, that was not as common in other cell types.

Next, the researchers studied NPCs at various points as they differentiated into other cell types in the laboratory. The level of the NPC signal decreased over time, while the levels of other markers common in neurons and astrocytes rose. The newly identified marker was more common in brain cells from embryonic mice than in those from adult mice. It also was more common in cells from the mouse hippocampus, a region where neurogenesis occurs constantly, than in cells from the brain's cortex, where new neurons are not normally

formed.

Dr. Maletic-Savatic, Dr. Enikolopov and their colleagues then gave adult mice a form of electrical stimulation that increases the amount of neurogenesis in the brain. They found that the marker they had identified increased significantly after the stimulation. Additional results indicated that the marker is probably a mixture of lipids (fatty acids), although the exact identity of the lipids, and how they function in NPCs, is still undetermined.

The researchers then developed a signal processing method that allowed them to separate the marker from other signals in the living brain. They transplanted NPCs into the cortex of the adult rat brain and found that they could clearly detect the marker in the area where the NPCs were injected. They also found that it increased after stimulation.

Finally, the investigators tested their MRS imaging technique in healthy people. They found major differences in the concentration of the marker between the hippocampus and the cortex. They also imaged the brains of pre-adolescents, adolescents, and adults and found that the marker decreased with age.

The findings suggest that the marker identified in these experiments can be used to detect NPCs and neurogenesis in the live human brain using MRS. They also show that NPCs decrease during brain development. Previous research had shown that neurogenesis decreases with age in animals, but this is the first study to demonstrate that it also decreases in the living human brain.

"This study identifies a novel biomarker and shows that we can use it to see progenitor cells in the live brain," Dr. Enikolopov says. "This protocol can now be used to study a variety of problems." For example, researchers might study people with depression to see if neurogenesis

correlates with alterations in depression or schizophrenia. The technique might also be used to study changes that occur in neurological diseases such as traumatic brain injury, stroke, epilepsy, and Parkinson's disease. It might even be useful for detecting cancer, because researchers believe some brain tumors are associated with aberrant proliferation of NPCs, Dr. Enikolopov adds.

The researchers are now planning studies that will test the usefulness of the new imaging technique in people with disease. They also hope to improve their understanding of how the lipids they detected function in NPCs and to refine the sensitivity of their technique.

Source: National Institute of Neurological Disorders and Stroke