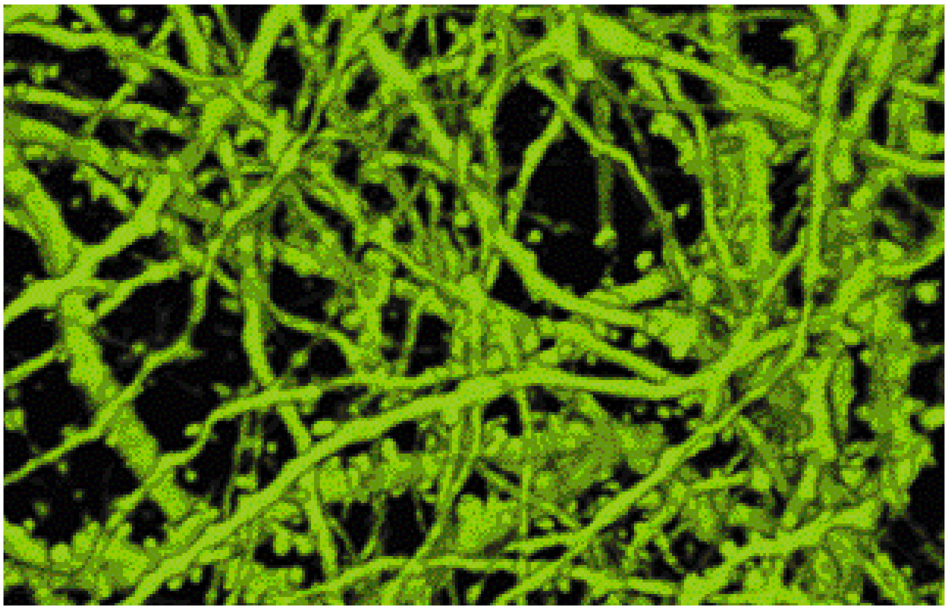
News from Medicine



Dendrites, long fingerlike extensions of nerve cells, can be seen above in this two-photon fluorescent micrgraph of a living mouse brain, as captured by Dr. Wen-Biao Gan.

Researchers Gain Insights into Learning and Self-Repair in the Ever-Dynamic Brain

The brain's remarkable plasticity—its ability to adapt in response to ever-changing experiences—has fascinated scientists for decades. Now a team of NYU researchers, led by Wen-Biao Gan, Ph.D., Assistant Professor of Physiology and Neuroscience, have captured images of this process that are helping them to unravel some of the mysteries of how brain cells remodel themselves as needed.

As a growing child learns about its world by interacting with its environment, the brain rapidly loses synapses. "Until puberty, you see a substantial loss of neuronal connections in the human brain, as well as in those of the monkey and mouse," says Dr. Gan. He believes this loss may be the fundamental process underlying the development and plasticity of the brain.

Dr. Gan likens learning to the sculpting process. "First there is a raw material, and then it is sculpted," he says. A lack of sensory experience in childhood appears to reduce the amount of this neuronal sculpting, according to a recent study in the journal *Nature* by Dr. Gan and his lab members Yi Zuo, Guang Yang, and Elaine Kwon.

The group used mice to demonstrate that sensory deprivation does indeed affect the loss of neurons that occurs during normal growth. The researchers employed a technique called two-photon fluorescence microscopy to look at living neurons in the brains of the mice. Dr. Gan looked at sites crucial to learning and memory called spines on the branches of neurons. Spines are where synapses, the gaps between neurons through which information travels, are formed.

Because mice rely heavily on their whiskers to experience their world, Dr. Gan altered their experience by trimming the whiskers on one side of the mice's snouts for two weeks. The spines of these mice were then compared to spines in mice of the same age with untrimmed whiskers. Young mice who kept their whiskers showed more spine loss than their whisker-trimmed litter mates.

The researchers found that the period of young adolescence to adulthood in mice was particularly susceptible to this kind of sensory deprivation. "We found that the refinement of the brain's structure was largely stopped or hindered," Dr. Gan says.

In the adult age group, short-term whisker trimming appeared to have little effect on spine loss or formation. However, when the sensory deprivation continued for two months, the effect was visible in adult animals too.

The effects of sensory deprivation can be reversed only partially as the animal ages, which suggests that "childhood experience has a long-lasting and perhaps permanent impact on later life," says Dr. Gan.

In another study, Dr. Gan and his colleagues used the same imaging technique to study self-repair in the brain, which is managed with the help of highly branched, motile microglia, cells that are part of the brain's immune system. When local injury is sustained, microglia actually cordon off the injured area, thus containing the damage.

Recent work, published in the journal *Nature Neuroscience*, has not only captured images of the microglia in action but, for the first time, has shown how their dynamic and quick response to injury is achieved.

Video images of mouse brains showed that within one minute of injury, branches of microglial cells appeared bulbous and enlarged. Over the next few minutes, the cells extended these branches toward the injured site. After about 30 minutes, the branches had fused into a spherical shield around the wound, containing it.

Surprisingly, the researchers also found that the molecule adenosine triphosphate (ATP), the main energy carrier in cells, acted as a mediator of microglial response to injury. The results of their experiments suggest that other cells in the brain, namely astrocytes, participate in recruiting microglial cells to the site of injury by releasing their own ATP. Astrocytes are the star-shaped members of the brain's glial cell family that support and influence neuronal activity.

"It is likely that astrocytes activate their neighbors to release more ATP, creating a chemical gradient that in turn attracts microglia toward the injury," says Dr. Gan. "It surprised us that astrocytes played this kind of role in amplifying the signal."

Dr. Gan's NYU collaborators on the microglial study were Michael Dustin, Ph.D., the Irene Diamond Associate Professor of Immunology and Associate Professor of Pathology, and Dan Littman, M.D., Ph.D., the Helen L. and Martin S. Kimmel Professor of Molecular Immunology at the Skirball Institute of Biomolecular Medicine and Professor of Pathology and Microbiology. ■

— Vivien Marx

New Computer Program Uses Brain Scans to Assess Risk of Alzheimer's Disease

Unfortunately, Alzheimer's disease is often diagnosed when the disorder is already well advanced and there is little that can be done to stall its progression. Now a brain-scan-based computer program developed by School of Medicine researchers may make it possible to diagnose the disease years earlier.

According to a new study by the NYU team, the computer program identified which healthy individuals would develop Alzheimer's as much as nine years before symptoms of the disease appeared. The program reveals below-normal energy use in an area of the brain called the hippocampus, a seahorse-shaped area of the brain associated with memory and learning. It diminishes in size as Alzheimer's disease progresses from mild cognitive impairment to full-blown dementia.

"This is the first demonstration that reduced metabolic activity in the hippocampus may be used to help predict future Alzheimer's disease," says Lisa Mosconi, Ph.D., a Research Scientist in the Department of Psychiatry, who developed the computer program. "Although our findings need to be replicated in other studies," she says, "our technique offers the possibility that we will be able to screen for Alzheimer's in individuals who aren't cognitively impaired."

Alzheimer's currently affects 4.5 million people in the United States, and it is expected to strike 14 million by 2050 as the population ages.

The technique grew out of years of research by Mony de Leon, Ed.D., Professor of Psychiatry and Director of the School's Center for Brain Health of the Silberstein Institute for Aging and Dementia. His group was the first to demonstrate with CT and later with MRI scans that the hippocampus shrinks as Alzheimer's disease progresses. However these scans do not provide a reliable way to accurately and quickly measure the hippocampus. The hippocampus is small and its size and shape are affected greatly in individuals with Alzheimer's, making it difficult to measure this region. The new computer program integrates MRI and PET scans, which measure energy use in the brain, to provide a way to accurately and quickly measure the hippocampus.

Dr. de Leon followed 53 normal subjects between the ages of 54 and 80 for at least nine years and in some cases for as long as 24 years as part of a longitudinal study. All subjects received two PET scans—one at baseline and a follow-up after three years. Thirty individuals had a second follow-up scan after another seven years. Altogether there were 136 PET scans.

Dr. Mosconi reanalyzed all 136 scans with the computer program and reported the results at a meeting of the Alzheimer's Association. Among those individuals who would later experience cognitive decline related to either mild cognitive impairment or to Alzheimer's, hippocampal glucose metabolism was significantly reduced 15 percent to 40 percent on the first scan, compared to controls. ■

— John Casey